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(71) Applicant *(for all designated States except US)*: **THE GENERAL HOSPITAL CORPORATION** [US/US]; 55 Fruit Street, Boston, MA 02114 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **AUSUBEL, Frederick, M.** [US/US]; 271 Lake Avenue, Newton, MA 02161 (US). **DRENKARD, Eliana** [AR/US]; 50 Massachusetts Avenue, Cambridge, MA 02139 (US).

(74) Agent: **DECAMP, James, D.**; Clark & Elbing LLP, 101 Federal Street, Boston, MA 02110 (US).

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(54) Title: REGULATORS OF BIOFILM FORMATION AND USES THEREOF

(57) Abstract: This invention relates to nucleic acid and amino acid sequences of genes regulating bacterial biofilm formation and to the use of these sequences as targets in the diagnosis, treatment, and prevention of bacterial infection and pathogenesis. In addition, the invention relates to screening methods for identifying modulators of bacterial biofilm formation and the development of antibacterial treatments.

REGULATORS OF BIOFILM FORMATION AND USES THEREOF

Background of the Invention

This application claims benefit of U.S. provisional applications 60/303,286 and 60/373,233, filed July 6, 2001 and April 16, 2002, respectively. The disclosures of which are hereby incorporated by reference.

This invention relates to nucleic acid and amino acid sequences of genes regulating bacterial biofilm formation and to the use of these sequences as targets in the diagnosis, treatment, and prevention of bacterial infection and pathogenesis. In addition, the invention relates to screening methods for identifying modulators of bacterial biofilm formation and the development of antibacterial treatments.

Bacteria possess the ability to form aggregated, organized, colonial communities called biofilms. Distinct from their free-living planktonic counterparts, bacterial cells that form biofilms secrete an exopolysacharide slime that surrounds and protects the bacterial colony. By adhering to each other and to surfaces or interfaces, these matrix-enclosed bacterial populations can cause any number of problems. By attaching to a variety of surfaces such as contact lenses, water pipes, hip replacements and food packaging, they can cause irritation, disease, immune rejection, and food poisoning.

In addition to attaching to abiotic surfaces, many biofilm-forming bacteria colonize living tissue where they cause serious infection. For example, *Pseudomonas aeruginosa* colonizes the lungs of cystic fibrosis (CF) patients as a biofilm. Chronic colonization of the airways by this bacterial pathogen leads to debilitating exacerbation of pulmonary infection and constitutes the major cause of morbidity and mortality in CF populations. Colonization of the CF lung by *P. aeruginosa* generally persists despite the use of long-term antibiotic therapy, since antibiotic treatment rarely results in complete eradication of the infection.

As current antibiotic therapies offer limited effectiveness in treating biofilm infection, a need exists for developing therapeutic agents that prevent biofilm formation. The discovery of polypeptides that regulate biofilm formation and polynucleotides encoding such polypeptides fulfills a need in the art by providing new compositions that are useful in the diagnosis, treatment, and prevention of bacterial infection and pathogenesis, as well as biofilm formation in both industrial and medical settings.

Summary of the Invention

As is described in more detail below, we have discovered a regulatory system that modulates microbial phenotypic switching. In one aspect, the invention features an isolated polypeptide that includes an amino acid sequence that is at least 50% (and preferably 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95-99%) identical to the amino acid sequence of PvrR (SEQ ID NO:2), wherein expression of the polypeptide, in a microorganism, affects phenotype-mediated antibiotic-resistance in the microorganism. In preferred embodiments, the polypeptide includes the amino acid sequence of PvrR (SEQ ID NO:2) or consists essentially of the amino acid sequence of PvrR (SEQ ID NO:2) or a fragment thereof.

In a related aspect, the invention features an isolated polypeptide fragment of an isolated polypeptide that includes an amino acid sequence having at least 50% identity to the amino acid sequence of PvrR (SEQ ID NO:2). In preferred embodiments, such a polypeptide fragment includes at least 300 contiguous amino acid residues of the amino acid sequence of PvrR (SEQ ID NO:2). In other embodiments, the fragment is at least 250 amino acid residues, 200 amino acid residues, or 100 amino acid residues of the amino acid sequence of PvrR (SEQ ID NO:2).

In another aspect, the invention features an isolated polynucleotide having at least 50% identity to the nucleotide sequence of *pvrR* (SEQ ID NO:1), wherein expression of the polynucleotide, in a microorganism, affects phenotype-mediated antibiotic-resistance in the microorganism. In preferred embodiments, the isolated polynucleotide includes the nucleotide sequence of *pvrR* (SEQ ID NO:1) or a

complement thereof. In yet other preferred embodiments, the polynucleotide consists essentially of the nucleotide sequence of *pvrR* (SEQ ID NO:1) or a fragment thereof.

In still other related aspects, the invention features a vector including any of the aforementioned isolated polynucleotides and a host cell that includes the vector.

The invention further features a variety of screening assays for identifying compounds that modulate phenotype-mediated antibiotic-resistance, biofilm formation, or biofilm-mediated antibiotic resistance. For example, the invention features a screening method that is useful for identifying a compound that modulates the gene expression of a regulator polynucleotide that affects phenotype-mediated antibiotic-resistance in a microorganism. Such a method includes the steps of: (a) providing a microbial cell (e.g., *Pseudomonas, Vibrio*, *Salmonella*, or *Staphylococcus*) that includes a polynucleotide having at least 50% identity to the nucleotide sequence of *pvrR* (SEQ ID NO:1)(or a nucleotide sequence that is substantially identical to *pvrR*), wherein expression of the polynucleotide, in the microbial cell, affects phenotype-mediated antibiotic-resistance in the microbial cell; (b) contacting the microbial cell with a compound; and (c) comparing the level of gene expression of the polynucleotide in the presence of the compound with the level of gene expression in the absence of the compound; wherein a measurable difference in gene expression indicates that the compound modulates gene expression of a regulator polynucleotide that affects phenotype-mediated antibiotic-resistance in a microorganism.

In preferred embodiments, the screening method identifies a compound that increases or decreases transcription of the regulator polynucleotide. In other embodiments, the screening method identifies a compound that increases or decreases translation of an mRNA transcribed from the regulator polynucleotide.

In other preferred embodiments, the microbial cell is a phenotypic variant (e.g., a small colony variant) having increased biofilm formation. Preferably, the small colony variant is a small colony variant of *Pseudomonas*, *Vibrio*, *Salmonella*, or *Staphylococcus*. In still other embodiments, the small colony variant is a rough small colony variant, for example, a rough small colony variant of *Pseudomonas, Vibrio,*

Salmonella, or *Staphylococcus*. In a preferred embodiment, the rough small colony variant is *Pseudomonas aeruginosa* PA14 RSCV.

In other preferred embodiments, the activity of the compound used in the screening assay is dependent upon the presence of the *pvrR* gene (SEQ ID NO:1) or a functional equivalent thereof. For example, the identified compound targets and interacts with the *pvrR* gene (SEQ ID NO:1) or a functional equivalent thereof. In still other preferred embodiments, the expression of the regulator polynucleotide mediates phenotypic switching of the microbial cell in the presence of a high concentration of an antibiotic. In other preferred embodiments of the screening method, the polypeptide is expressed using an isolated polynucleotide that expresses a polypeptide having an amino acid sequence having at least 50% identity to the amino acid sequence of PvrR (SEQ ID NO:2) or a fragment thereof.

In another aspect, the invention features a screening method for identifying a compound that modulates an activity of a polypeptide that affects phenotype-mediated antibiotic-resistance in a microorganism. The method, in general, includes the steps of: (a) providing a microbial cell expressing a polypeptide having at least 50% identity to the amino acid sequence of PvrR (SEQ ID NO:2) (or a polypeptide that is substantially identical to PvrR), wherein expression of the polypeptide, in the microbial cell, affects phenotype-mediated antibiotic-resistance in the microbial cell; (b) contacting the microbial cell with a compound; and (c) comparing an activity of the polypeptide in the presence of the compound with the activity in the absence of the compound; wherein a measurable difference in the activity indicates that the compound modulates the activity of the polypeptide that affects phenotype-mediated antibiotic-resistance in a microorganism. In preferred embodiments, the screening method identifies a compound that increases or decreases the activity of the polypeptide. Comparison of the activity of the polypeptide includes a variety of standard biochemical analyses including immunological assays.

In preferred embodiments, the microbial cell utilized in the screening assay is a phenotypic variant (e.g., *Pseudomonas aeruginosa* PA14 RSCV) having increased biofilm formation relative to wild-type.

In other preferred embodiments, the regulator polypeptide is an isolated polypeptide that includes an amino acid sequence having at least 50% identity to the amino acid sequence of PvrR (SEQ ID NO:2) (or a polypeptide that is substantially identical to PvrR). In particular, such a polypeptide has the ability to regulate phenotypic switching; to regulate biofilm-mediated antibiotic-resistance; to mediate phenotypic switching of the microbial cell in the presence of a high concentration of an antibiotic; or to affect susceptibility of the microbial cell to antibiotic treatment; or to regulate, or mediate, or affect, or any combination of the aforementioned activities thereof. In other preferred embodiments, the regulator polypeptide is an element of a two-component regulatory system. In yet other preferred embodiments, the polypeptide is expressed by an isolated polynucleotide having at least 50% identity to the nucleotide sequence of *pvrR* (SEQ ID NO:1) or a fragment thereof.

Typically, the activity of the compound identified in the screening assay is dependent upon the presence of the PvrR polypeptide (SEQ ID NO:2) or a functional equivalent thereof. In particular aspects of the screening assay, the compound targets the PvrR polypeptide (SEQ ID NO:2) or a functional equivalent thereof.

In another aspect, the invention features a screening method for identifying a compound that modulates microbial biofilm formation. This method, in general, includes the steps of: (a) culturing a microbial cell (e.g., *Pseudomonas*, *Vibrio*, *Salmonella*, or *Staphylococcus*) that includes a polypeptide having at least 50% identity to the amino acid sequence of PvrR (SEQ ID NO:2) (or a polypeptide that is substantially identical to PvrR), wherein the microbial cell, upon culturing, forms a biofilm; (b) contacting the microbial cell with a compound; and (c) comparing microbial biofilm formation in the presence of the compound with microbial biofilm formation in the absence of the compound; wherein a measurable difference in the microbial biofilm formation indicates that the compound modulates biofilm formation.

In preferred embodiments, the screening method identifies a compound that increases or decreases biofilm formation. Typically, such biofilm formation is measured by using any standard method, for example, by assaying microbial aggregation (e.g., by using a microscope); using a salt aggregation test; or by using an attachment assay.

In preferred embodiments, the microbial cell is a phenotypic variant having increased biofilm formation when compared to its wild-type such as a small colony variant of *Pseudomonas*, *Vibrio*, *Salmonella*, or *Staphylococcus*. In other preferred embodiments, the small colony variant is a rough small colony variant of *Pseudomonas*, *Vibrio*, or *Salmonella*. In a preferred embodiment, the rough small colony variant is *Pseudomonas aeruginosa* PA14 RSCV.

In yet other preferred embodiments, the activity of the compound utilized in the screening assay is dependent upon the presence of PvrR polypeptide (SEQ ID NO: 2) or a functional equivalent thereof. For example, the identified compound targets and interacts with the PvrR polypeptide (SEQ ID NO:2) or a functional equivalent thereof, resulting in increasing or decreasing its functional activity.

In still another embodiment, the expression of the polypeptide mediates phenotypic switching of the microbial cell in the presence of a high concentration of an antibiotic.

In another embodiment, the polypeptide is an isolated polypeptide that includes an amino acid sequence having at least 50% identity to the amino acid sequence of PvrR (SEQ ID NO:2), wherein expression of the polypeptide, in a microorganism, affects phenotype-mediated antibiotic-resistance in the microorganism.

In still another aspect, the invention features a method of treating a microbial infection involving a microorganism that forms a biofilm in a mammal. The method, in general, includes administering to the mammal a therapeutically-effective amount of a compound that induces or represses expression or activity of a polypeptide that includes an amino acid sequence having at least 50% identity to the amino acid sequence of PvrR (SEQ ID NO:2) (or a polypeptide that is substantially identical to PvrR) or a fragment thereof, wherein expression of the polypeptide or the fragment thereof, in a microorganism, affects phenotype-mediated antibiotic-resistance in the microorganism.

In preferred embodiments, the method further includes administering to the mammal a therapeutically-effective amount of an antibiotic. The treatment is particularly useful for treating patients having cystic fibrosis or a chronic microbial

infection or both. In other preferred embodiments, the microorganism treated using the method belongs to the genus *Pseudomonas*, *Vibrio*, *Salmonella*, or *Staphylococcus*.

In yet another aspect, the invention features a method of cleaning, disinfecting, or decontaminating a surface at least partially covered by a microorganism that forms a biofilm, the method involving contacting the microorganism with a cleaning composition including a compound that induces or represses expression or activity of a polypeptide that includes an amino acid sequence having at least 50% identity to the amino acid sequence of PvrR (SEQ ID NO:2) (or a polypeptide that is substantially identical to PvrR) or fragment thereof, wherein expression of the polypeptide or the fragment thereof, in a microorganism, affects phenotype-mediated antibiotic-resistance in the microorganism.

In yet another aspect, the invention features a screening method for identifying a compound that decreases pathogenicity of an antibiotic-resistant phenotypic variant. The method, in general, includes the steps of: (a) contacting an antibiotic-resistant phenotypic variant with a candidate compound; and (b) measuring reversion of the antibiotic-resistant phenotypic variant to a wild-type phenotype, an increase in reversion indicating that the compound decreases pathogenicity of the antibiotic-resistant phenotypic variant. In preferred embodiments, the antibiotic-resistant phenotypic variant is cultured in the absence of an antibiotic, has increased biofilm formation; is a rough small colony variant; is a hyperpiliated variant; has increased hydrophobicity; has an alteration in a surface component; or is a pathogen such as a Gram positive bacterium (e.g., *Staphylococcus*) or a Gram negative bacterium (e.g., *Vibrio*, *Pseudomonas*, or *Salmonella*).

In another aspect, the invention features a screening method for identifying a compound that decreases pathogenicity of an antibiotic-resistant phenotypic variant. The method, in general, includes the steps of: (a) culturing an antibiotic-resistant phenotypic variant with a candidate compound in the presence of an antibiotic; and (b) comparing the number of antibiotic-resistant phenotypic variants in the presence of the compound to the number of antibiotic-resistant phenotypic variants in the absence of the compound, a decrease in the number of the antibiotic-resistant phenotypic variants in the

presence of the compound indicating that the compound decreases pathogenicity of the antibiotic-resistant phenotypic variant.

In yet another aspect, the invention features a screening method for identifying a polynucleotide encoding a regulator polypeptide, the method including the steps of: (a) providing a mutagenized microbe; (b) culturing the mutagenized microbe in the presence of an antibiotic; and (c) comparing the mutagenized microbe with a control wild-type microbe, wherein a change in the number of phenotypic variants identifies the mutagenized microbe as having a mutation in a polynucleotide encoding a regulator polypeptide. In preferred embodiments, the phenotypic variant is a small colony variant.

In another aspect, the invention features a screening method for identifying a polynucleotide encoding a regulator polypeptide that modulates an antibiotic-resistant phenotype of a microorganism. The method, in general, includes the steps of: (a) identifying an antibiotic-resistant phenotypic variant of a microorganism including a first phenotype; (b) mutagenizing the antibiotic-resistant phenotypic variant of the microorganism, thereby generating a mutated phenotypic variant of the microorganism; and (c) selecting the mutated phenotypic variant of step (b) having a second phenotype, other than the first phenotype of the antibiotic-resistant phenotypic variant, wherein the second phenotype identifies a mutation in the mutated phenotypic variant of step (b); and (d) using the mutation for identifying a polynucleotide encoding a regulator polypeptide that modulates an antibiotic-resistant phenotype of a microorganism. In preferred embodiments, the second phenotype includes a wild-type phenotype.

In yet another aspect, the invention features a screening method for identifying a polynucleotide encoding a regulator polypeptide that modulates phenotype-mediated antibiotic-resistance of a microorganism. The method, in general, includes the steps of: (a) transforming an antibiotic-resistant phenotypic variant of a microorganism with a candidate polynucleotide encoding a regulator polypeptide; and (b) culturing the transformed antibiotic-resistant phenotypic variant of a microorganism under conditions suitable for expression of the regulator polypeptide; and (c) measuring reversion of the transformed antibiotic-resistant phenotypic variant of the microorganism to a wild-type

phenotype, an increase in reversion identifies the polynucleotide as encoding a regulator polypeptide that modulates phenotype-mediated antibiotic-resistance.

In preferred embodiments, the polynucleotide encodes a regulator polypeptide that modulates a phenotypic switch from an antibiotic-resistant phenotype to an antibiotic-susceptible phenotype. In other preferred embodiments, the candidate polynucleotide has at least 50% identity to the nucleotide sequence of *pvrR* (SEQ ID NO:1) (or a polynucleotide sequence that is substantially identical to *pvrR*). In other embodiments, the candidate polynucleotide sequence is substantially identical to any one of the polynucleotides shown in Figures 5B, 5C, 6A-6K, and 7A-7E . In other preferred embodiments, the candidate polynucleotide encodes a polypeptide that is an element of a two-component regulatory system.

In another aspect, the invention features an isolated polypeptide including an amino acid sequence that is substantially identical to the amino acid sequence of any one the polypeptides shown in Figures 5E (SEQ ID NO: 4) and 6L-6V (SEQ ID NOS: 19-29), each of which are encoded by a polynucleotide of the ORF1 region.

For example, with respect to the ORF1 region, the invention features an isolated polypeptide that includes an amino acid sequence that is at least 50% (and preferably 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95-99%) identical to the amino acid sequence of the polypeptide shown in Figure 5E (SEQ ID NO: 4) or to a polypeptide shown in Figures 6L-6V (SEQ ID NOS: 19-29), wherein expression of the polypeptide, in a microorganism, affects phenotype-mediated antibiotic-resistance in the microorganism. Preferably, the polypeptide includes the amino acid sequence shown in Figure 5E or consists essentially of the amino acid sequence shown in Figure 5E or a fragment thereof.

In a related aspect, the invention features an isolated polypeptide fragment of an isolated polypeptide that includes an amino acid sequence having at least 50% identity to the amino acid sequence the polypeptide shown in Figure 5E or to a polypeptide shown in any one of Figures 6L-6V. In preferred embodiments, such a polypeptide fragment includes at least 400 contiguous amino acid residues of the amino acid sequence shown in any one of Figures 5E and 6L-6V. In other embodiments, the fragment is at least 300

amino acid residues, 200 amino acid residues, or 100 amino acid residues of the polypeptides shown in Figures 5E and 6L-6V.

In another aspect, the invention features an isolated polynucleotide molecule including a sequence substantially identical to any one of the polynucleotides shown in Figures 5B (SEQ ID NO:3) and 6A-6K (SEQ ID NOS: 8-18), which are found in the ORF1 region. In preferred embodiments, the isolated polynucleotide molecule has at least 45%, 50%, 60%, 70%, 80%, 90%, or even 95-99% identity to any one of these isolated molecules.

For example, with respect to the ORF1 region, the invention features an isolated polynucleotide having at least 50% identity to the nucleotide sequence shown in Figure 5B or to any one of the nucleotide sequences shown in Figures 6A-6K, wherein expression of the polynucleotide, in a microorganism, affects phenotype-mediated antibiotic-resistance in the microorganism. In preferred embodiments, the isolated polynucleotide includes the nucleotide sequence shown in Figure 5B or a complement thereof. In yet other preferred embodiments, the polynucleotide consists essentially of the nucleotide sequence shown in Figure 5B or a fragment thereof.

In still other related aspects, the invention features a vector including any of the aforementioned isolated polynucleotides and a host cell that includes the vector.

The invention further features a variety of screening assays for identifying compounds that modulate phenotype-mediated antibiotic-resistance, biofilm formation, or biofilm-mediated antibiotic resistance. For example, the invention features a screening method that is useful for identifying a compound that modulates the gene expression of a regulator polynucleotide that affects phenotype-mediated antibiotic-resistance in a microorganism. Such a method includes the steps of: (a) providing a microbial cell (e.g., *Pseudomonas, Vibrio*, *Salmonella*, or *Staphylococcus*) that includes a polynucleotide that is substantially identical to any one of the nucleotide sequences shown in Figures 5B or 6A-6K (or a polynucleotide having at least 40% identity to any one of these sequences), wherein expression of the polynucleotide, in the microbial cell, affects phenotype-mediated antibiotic-resistance in the microbial cell; (b) contacting the microbial cell with a compound; and (c) comparing the level of gene expression of the

polynucleotide in the presence of the compound with the level of gene expression in the absence of the compound; wherein a measurable difference in gene expression indicates that the compound modulates gene expression of a regulator polynucleotide that affects phenotype-mediated antibiotic-resistance in a microorganism.

In preferred embodiments, the screening method identifies a compound that increases or decreases transcription of the regulator polynucleotide. In other embodiments, the screening method identifies a compound that increases or decreases translation of an mRNA transcribed from the regulator polynucleotide.

In other preferred embodiments, the microbial cell is a phenotypic variant (e.g., a small colony variant) having increased biofilm formation. Preferably, the small colony variant is a small colony variant of *Pseudomonas*, *Vibrio*, *Salmonella*, or *Staphylococcus*. In still other embodiments, the small colony variant is a rough small colony variant, for example, a rough small colony variant of *Pseudomonas, Vibrio*, *Salmonella*, or *Staphylococcus*. In a preferred embodiment, the rough small colony variant is *Pseudomonas aeruginosa* PA14 RSCV.

In other preferred embodiments, the activity of the compound used in the screening assay is dependent upon the presence of any one of the polynucleotides shown in Figures 5B or 6A-6K, or a functional equivalent thereof. For example, the identified compound targets any one of the polynucleotides shown in Figures 5B or 6A-6K or a functional equivalent thereof. In still other preferred embodiments, the expression of the regulator polynucleotide mediates phenotypic switching of the microbial cell in the presence of a high concentration of an antibiotic. In other preferred embodiments of the screening method, the polypeptide is expressed using an isolated polynucleotide that encodes a polypeptide that is substantially identical to any one of the polynucleotides shown Figures 5B and 6A-6K or a fragment thereof.

In another aspect, the invention features a screening method for identifying a compound that modulates an activity of a polypeptide that affects phenotype-mediated antibiotic-resistance in a microorganism. The method, in general, includes the steps of: (a) providing a microbial cell expressing a polypeptide that is substantially identical to any one of the polypeptides shown in Figures 5E and 6L-6V (or a polypeptide having at

least 40% identity to any one of these sequences), wherein expression of the polypeptide, in the microbial cell, affects phenotype-mediated antibiotic-resistance in the microbial cell; (b) contacting the microbial cell with a compound; and (c) comparing an activity of the polypeptide in the presence of the compound with the activity in the absence of the compound; wherein a measurable difference in the activity indicates that the compound modulates the activity of the polypeptide that affects phenotype-mediated antibiotic-resistance in a microorganism. In preferred embodiments, the screening method identifies a compound that increases or decreases the activity of the polypeptide. Comparison of the activity of the polypeptide includes a variety of standard biochemical analyses including immunological assays.

In preferred embodiments, the microbial cell utilized in the screening assay is a phenotypic variant (e.g., *Pseudomonas aeruginosa* PA14 RSCV) having increased biofilm formation.

In other preferred embodiments, the regulator polypeptide is an isolated polypeptide that includes an amino acid sequence that is substantially identical to any one of the polypeptides shown in Figures 5E and 6L-6V (or a polypeptide having at least 40% identity to any one of these sequences). In particular, such a polypeptide has the ability to regulate phenotypic switching; to regulate biofilm-mediated antibiotic-resistance; to mediate phenotypic switching of the microbial cell in the presence of a high concentration of an antibiotic; or to affect susceptibility of the microbial cell to antibiotic treatment; or any combination thereof. In other preferred embodiments, the regulator polypeptide is an element of a two-component regulatory system. In yet other preferred embodiments, the polypeptide is expressed by an isolated polynucleotide that is substantially identical to any one of the nucleotide sequences shown in Figures 5B and 6A-6K (or a polynucleotide having at least 40% identity to any one of these sequences) or a fragment thereof, upon which the activity of the regulator polypeptide is increased or decreased.

Typically, the activity of the compound identified in the screening assay is dependent upon the presence of any one of the polypeptides shown in Figures 5E and 6L-6V or a functional equivalent thereof. In particular aspects of the screening assay,

the compound targets or interacts with any one of the polypeptides shown in Figures 5E and 6L-6V or a functional equivalent thereof.

In another aspect, the invention features a screening method for identifying a compound that modulates microbial biofilm formation. This method, in general, includes the steps of: (a) culturing a microbial cell (e.g., *Pseudomonas*, *Vibrio*, *Salmonella*, or *Staphylococcus*) that includes a polypeptide that is substantially identical to any one of the polypeptides shown in Figures 5E and 6L-6V (or a polypeptide having at least 40% identity to any one of these sequences), wherein the microbial cell, upon culturing, forms a biofilm; (b) contacting the microbial cell with a compound; and (c) comparing microbial biofilm formation in the presence of the compound with microbial biofilm formation in the absence of the compound; wherein a measurable difference in the microbial biofilm formation indicates that the compound modulates biofilm formation.

In preferred embodiments, the screening method identifies a compound that increases or decreases biofilm formation. Typically, such biofilm formation is measured by using any standard method, for example, by assaying microbial aggregation (e.g., by using a microscope); using a salt aggregation test; or by using an attachment assay.

In preferred embodiments, the microbial cell is a phenotypic variant having increased biofilm formation when compared to its wild-type such as a small colony variant of *Pseudomonas*, *Vibrio*, *Salmonella*, or *Staphylococcus*. In other preferred embodiments, the small colony variant is a rough small colony variant of *Pseudomonas*, *Vibrio*, or *Salmonella*.

In yet other preferred embodiments, the activity of the compound utilized in the screening assay is dependent upon the presence of the polypeptide or a functional equivalent thereof. For example, the identified compound targets or interacts with the polypeptide or a functional equivalent thereof, resulting in increasing or decreasing its functional activity.

In still another embodiment, the expression of the polypeptide mediates phenotypic switching of the microbial cell in the presence of a high concentration of an antibiotic.

In another embodiment, the polypeptide is an isolated polypeptide that includes an amino acid sequence that is substantially identical to any one of the polypeptides shown in Figures 5E and 6L-6V (or a polypeptide having at least 40% identity to any one of these sequences), wherein expression of the polypeptide, in a microorganism, affects phenotype-mediated antibiotic-resistance in the microorganism.

In still another aspect, the invention features a method of treating a microbial infection involving a microorganism that forms a biofilm in a mammal. The method, in general, includes administering to the mammal a therapeutically-effective amount of a compound that induces or represses expression or activity of a polypeptide that includes a polypeptide that is substantially identical to any one of the polypeptides shown in Figures 5E and 6L-6V or a fragment thereof (or a polypeptide having at least 40% identity to any one of these sequences), wherein expression of the polypeptide or the fragment thereof, in a microorganism, affects phenotype-mediated antibiotic-resistance in the microorganism.

In another aspect, the invention features an isolated polypeptide including an amino acid sequence that is substantially identical to the amino acid sequence of any one of the polypeptides shown in Figures 5F and Figures 7F-7J, each of which are encoded by a polynucleotide of the ORF3 region.

For example, with respect to the ORF3 region, the invention features an isolated polypeptide that includes an amino acid sequence that is at least 50% (and preferably 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95-99%) identical to the amino acid sequence of any one of the polypeptides shown in Figures 5F (SEQ ID NO:6) and 7F-7J (SEQ ID NOS:35-39), wherein expression of the polypeptide, in a microorganism, affects phenotype-mediated antibiotic-resistance in the microorganism. Preferably, the polypeptide includes the amino acid sequence shown in Figure 7J (SEQ ID NO:39) or consists essentially of the amino acid sequence shown in Figures 5F (SEQ ID NO:6) and 7F-7I (SEQ ID NOS:35-38) or a fragment thereof.

In a related aspect, the invention features an isolated polypeptide fragment of an isolated polypeptide that includes an amino acid sequence having at least 50% identity to the amino acid sequence of the polypeptides shown in Figures 5F and 7F-7J. In

preferred embodiments, such a polypeptide fragment includes at least 300 contiguous amino acid residues of the amino acid sequence shown in any one of Figures 5F and 7F-7J. In other embodiments, the fragment is at least 200 amino acid residues, or 100 amino acid residues of the polypeptides shown in Figures 5F and 7F-7J.

In another aspect the invention features an isolated polynucleotide molecule including a sequence substantially identical to any one of the polynucleotides shown in Figures 5C (SEQ ID NO:5) and 7A-7E (SEQ ID NOS:30-34). In preferred embodiments, the isolated polynucleotide molecule has at least 45%, 50%, 60%, 70%, 80%, 90%, or even 95% identity to any one of these molecules.

For example with respect to the ORF3 region, the invention features an isolated polynucleotide having at least 50% identity to any one of the nucleotide sequences shown in Figures 5C and 7A-7E, wherein expression of the polynucleotide, in a microorganism, affects phenotype-mediated antibiotic-resistance in the microorganism. In preferred embodiments, the isolated polynucleotide includes the nucleotide sequence shown in Figure 5C or a complement thereof. In yet other preferred embodiments, the polynucleotide consists essentially of the nucleotide sequence shown in Figure 5C or a fragment thereof.

In still other related aspects, the invention features a vector including any of the aforementioned isolated polynucleotides and a host cell that includes the vector.

The invention further features a variety of screening assays for identifying compounds that modulate phenotype-mediated antibiotic-resistance, biofilm formation, or biofilm-mediated antibiotic resistance. For example, the invention features a screening method that is useful for identifying a compound that modulates the gene expression of a regulator polynucleotide that affects phenotype-mediated antibiotic-resistance in a microorganism. Such a method includes the steps of: (a) providing a microbial cell (e.g., *Pseudomonas, Vibrio*, *Salmonella*, or *Staphylococcus*) that includes a polynucleotide substantially identical to the nucleotide sequences shown in Figures 5C and 7A-7E (or a polynucleotide having at least 45% identity to any one of these sequences), wherein expression of the polynucleotide, in the microbial cell, affects phenotype-mediated antibiotic-resistance in the microbial cell; (b) contacting the

microbial cell with a compound; and (c) comparing the level of gene expression of the polynucleotide in the presence of the compound with the level of gene expression in the absence of the compound; wherein a measurable difference in gene expression indicates that the compound modulates gene expression of a regulator polynucleotide that affects phenotype-mediated antibiotic-resistance in a microorganism.

In preferred embodiments, the screening method identifies a compound that increases or decreases transcription of the regulator polynucleotide. In other embodiments, the screening method identifies a compound that increases or decreases translation of an mRNA transcribed from the regulator polynucleotide.

In other preferred embodiments, the microbial cell is a phenotypic variant (e.g., a small colony variant) having increased biofilm formation. Preferably, the small colony variant is a small colony variant of *Pseudomonas*, *Vibrio*, *Salmonella*, or *Staphylococcus*. In still other embodiments, the small colony variant is a rough small colony variant, for example, a rough small colony variant of *Pseudomonas, Vibrio*, *Salmonella*, or *Staphylococcus*. In a preferred embodiment, the rough small colony variant is *Pseudomonas aeruginosa* PA14 RSCV.

In other preferred embodiments, the activity of the compound used in the screening assay is dependent upon the presence of any one of the polynucleotides shown in Figures 5C and 7A-7E or a functional equivalent thereof. For example, the identified compound targets or interacts with any one of the polynucleotides shown in Figures 5C and 7A-7E or a functional equivalent thereof. In still other preferred embodiments, the expression of the regulator polynucleotide mediates phenotypic switching of the microbial cell in the presence of a high concentration of an antibiotic. In other preferred embodiments of the screening method, the polypeptide is expressed from an isolated polynucleotide that expresses a polypeptide that includes an amino acid sequence having at least 50% identity to any one of the amino acid sequences shown in Figures 5F and 7F-7J or a fragment thereof.

In another aspect, the invention features a screening method for identifying a compound that modulates an activity of a polypeptide that affects phenotype-mediated antibiotic-resistance in a microorganism. The method, in general, includes the steps of:

(a) providing a microbial cell expressing a polypeptide that is substantially identical to any one of the polypeptides shown in Figures 5F and 7F-7J (or a polypeptide having at least 45% identity to any one of these sequences), wherein expression of the polypeptide, in the microbial cell, affects phenotype-mediated antibiotic-resistance in the microbial cell; (b) contacting the microbial cell with a compound; and (c) comparing an activity of the polypeptide in the presence of the compound with the activity in the absence of the compound; wherein a measurable difference in the activity indicates that the compound modulates the activity of the polypeptide that affects phenotype-mediated antibiotic-resistance in a microorganism. In preferred embodiments, the screening method identifies a compound that increases or decreases the activity of the polypeptide. Comparison of the activity of the polypeptide includes a variety of standard biochemical analyses including immunological assays.

In preferred embodiments, the microbial cell utilized in the screening assay is a phenotypic variant (e.g., *Pseudomonas aeruginosa* PA14 RSCV) having increased biofilm formation.

In other preferred embodiments, the regulator polypeptide is an isolated polypeptide that includes an amino acid sequence that is substantially identical to any one of the polypeptides shown in Figures 5F and 7F-7J (or a polypeptide having at least 45% identity to any one of these sequences). In particular, such a polypeptide has the ability to regulate phenotypic switching; to regulate biofilm-mediated antibiotic-resistance; to mediate phenotypic switching of the microbial cell in the presence of a high concentration of an antibiotic; or to affect susceptibility of the microbial cell to antibiotic treatment; or any combination thereof. In other preferred embodiments, the regulator polypeptide is an element of a two-component regulatory system. In yet other preferred embodiments, the polypeptide is expressed by an isolated polynucleotide substantially identical to any one of the nucleotide sequences shown in Figures 5C and 7A-7E (or by a polynucleotide having at least 45% identity to any one of these sequences) or a fragment thereof, upon which the activity of the regulator polypeptide is increased or decreased.

Typically, the activity of the compound identified in the screening assay is dependent upon the presence of any one of the polypeptides shown in Figures 5F and 7F-7J or a functional equivalent thereof. In particular aspects of the screening assay, the compound targets and interacts with the polypeptide of Figures 5F and 7F-7J or a functional equivalent thereof.

In another aspect, the invention features a screening method for identifying a compound that modulates microbial biofilm formation. This method, in general, includes the steps of: (a) culturing a microbial cell (e.g., *Pseudomonas*, *Vibrio*, *Salmonella*, or *Staphylococcus*) that includes a polypeptide substantially identical to any one of the amino acid sequences shown in Figures 5F and 7F-7J (or a polypeptide having at least 45% identity to any one of these sequences), wherein the microbial cell, upon culturing, forms a biofilm; (b) contacting the microbial cell with a compound; and (c) comparing microbial biofilm formation in the presence of the compound with microbial biofilm formation in the absence of the compound; wherein a measurable difference in the microbial biofilm formation indicates that the compound modulates biofilm formation.

In preferred embodiments, the screening method identifies a compound that increases or decreases biofilm formation. Typically, such biofilm formation is measured by using any standard method, for example, by assaying microbial aggregation (e.g., by using a microscope); using a salt aggregation test; or by using an attachment assay.

In preferred embodiments, the microbial cell is a phenotypic variant having increased biofilm formation when compared to its wild-type such as a small colony variant of *Pseudomonas*, *Vibrio*, *Salmonella*, or *Staphylococcus*. In other preferred embodiments, the small colony variant is a rough small colony variant of *Pseudomonas*, *Vibrio*, or *Salmonella*.

In yet other preferred embodiments, the activity of the compound utilized in the screening assay is dependent upon the presence of the polypeptide or a functional equivalent thereof. For example, the identified compound targets and interacts with the polypeptide or a functional equivalent thereof, resulting in increasing or decreasing its functional activity.

In still another embodiment, the expression of the polypeptide mediates phenotypic switching of the microbial cell in the presence of a high concentration of an antibiotic.

In another embodiment, the polypeptide is an isolated polypeptide that includes an amino acid sequence that is substantially identical to any one of the amino acid sequences shown in Figures 5F and 7F-7J (or a polypeptide having at least 45% identity to any one of these sequences), wherein expression of the polypeptide, in a microorganism, affects phenotype-mediated antibiotic-resistance in the microorganism.

In still another aspect, the invention features a method of treating a microbial infection involving a microorganism that forms a biofilm in a mammal. The method, in general, includes administering to the mammal a therapeutically-effective amount of a compound that induces or represses expression or activity of a polypeptide that includes an amino acid sequence that is substantially identical to any one of the amino acid sequences shown in Figures 5F and 7F-7J or a fragment thereof (or a polypeptide having at least 45% identity to any one of these sequences), wherein expression of the polypeptide or the fragment thereof, in a microorganism, affects phenotype-mediated antibiotic-resistance in the microorganism.

In preferred embodiments, the method further includes administering to the mammal a therapeutically-effective amount of an antibiotic. The treatment is particularly useful for treating patients having cystic fibrosis or a chronic infection or both. In other preferred embodiments, the microorganism treated using the method belongs to the genus *Pseudomonas*, *Vibrio*, *Salmonella,* or *Staphylococcus*.

In yet another aspect, the invention features a method of cleaning, disinfecting, or decontaminating a surface at least partially covered by a microorganism that forms a biofilm, the method involving contacting the microorganism with a cleaning composition including a compound that induces or represses expression or activity of a polypeptide that includes an amino acid sequence having at least 50% identity to the amino acid sequence of Figures 5E, 5F, 6L-6V, and 7F-7J or fragment thereof (or a polypeptide that is substantially identical to any one of these polypeptides), wherein

expression of the polypeptide or the fragment thereof, in a microorganism, affects phenotype-mediated antibiotic-resistance in the microorganism.

The invention also features methods for identifying compounds useful for treating a patient having a biofilm infection. The method includes the steps of contacting a biofilm *in vitro* with (i) an antibiotic and (ii) a candidate compound (e.g., a compound that modulates the expression, at the transcriptional, post-transcriptional, translational, or post-translational levels, of a polynucleotide having at least 50% identity to any of the polynucleotides described herein (or that is substantially identical to a polynucleotide described herein), and determining whether the biofilm grows more slowly than (a) biofilm cells contacted with an antibiotic but not contacted with the test compound, and (b) biofilm cells contacted with the candidate compound but not with the antibiotic. In another embodiment, the biofilm is contacted with two or more different antibiotics. Exemplary antibiotics useful in the method include amikacin, aminoglicosides (e.g., tobramycin), aztreonam, carbenicillin, cephalosporines (e.g., ceftazidime or cefipime), chloramphenicol, gentamicin, levofloxacin, meropenem, piperacillin, tazobactam, tetracycline, and quinolones (e.g., ciprofloxacin). A candidate compound that reduces biofilm formation in the presence of an antibiotic (or combination of different antibiotics), but does not decrease biofilm formation in the absence of the antibiotic (or combination of different antibiotics), is a compound that is useful in combination therapy for treating a patient having a biofilm infection.

The invention further features a method for treating a patient having a biofilm infection, by administering to the patient an antibiofilm combination therapy that includes a compound identified as modulating expression, at the transcriptional, post-transcriptional, translational, or post-translational levels, of a polynucleotide having at least 50% identity to any of the polynucleotides described herein (or that is substantially identical to a polynucleotide described herein) and one or more antibiotics, including, but not limited to, amikacin, aminoglicosides (e.g., tobramycin), aztreonam, carbenicillin, cephalosporines (e.g., ceftazidime or cefipime), chloramphenicol, gentamicin, levofloxacin, meropenem, piperacillin, tazobactam, tetracycline, and

quinolones (e.g., ciprofloxacin), simultaneously or within a period of time (e.g., 14 to 21 days) sufficient to inhibit the growth of the biofilm.

Preferably, the compound and antibiotic are administered within fifteen days of each other, more preferably within five or ten days of each other, and most preferably within twenty-four hours of each other or even simultaneously. Exemplary biofilms treated according to any of the methods described herein are those formed by bacteria, including but not limited to, *Pseudomonas*, *Staphylococcus*, *Salmonella*, *Vibrio*, *Haemophilus*, *Mycobacterium*, *Helicobacter*, *Burkholderia*, or *Streptococci*.

In a related aspect, the invention also features a method for treating a patient having a biofilm such as one formed from *Pseudomonas* (e.g., *Pseudomonas aeruginosa*). In this method, a patient is administered (a) a first compound (e.g., a compound that modulates the expression, at the transcriptional, post-transcriptional, translational, or post-translational; of a polynucleotide having at least 50% identity to a polynucleotide described herein (or that is substantially identical to a polynucleotide described herein)), and (b) one or more antibiotics (such as amikacin, aminoglicosides (e.g., tobramycin), aztreonam, carbenicillin, cephalosporines (e.g., ceftazidime or cefipime), chloramphenicol, gentamicin, levofloxacin, meropenem, piperacillin, tazobactam, tetracycline, and quinolones (e.g., ciprofloxacin). If desired, the therapy includes administration of two antibiotics according to standard methods known in the art. Such dual antibiotic combinations most preferably include high-dose tobramycin plus meropenem, meropenem plus ciprofloxacin, or tobramycin (4 μg/ml), or cefipime. Other preferred combinations include piperacillin plus tazobactam, or piperacillin plus ciprofloxacin. The antibiotic and compound combination therapy are preferably administered simultaneously or within a period of time sufficient to inhibit the growth of the biofilm.

In any of the foregoing treatments, the compound and antibiotic included in the combination therapy are preferably administered to the patient as part of a pharmaceutical composition that also includes a pharmaceutically acceptable carrier. Preferred modes of administration include intramuscular, intravenous, inhalation, and oral administration, or a combination thereof.

The antibiofilm combinations of the invention can also be part of a pharmaceutical kit. Preferably, the first compound (e.g., a compound identified as modulating expression, at the transcriptional, post-transcriptional, translational, or post-translational levels, of a polynucleotide or polypeptide having at least 50% identity to any one of the polynucleotide or polypeptide sequences described herein (or that is substantially identical to any one of the polynucleotides or polypeptides described herein)) and the second compound, an antibiotic, are formulated together or separately and in individual dosage amounts.

Combination therapy may be provided wherever antibiotic treatment is performed: at home, the doctor's office, a clinic, a hospital's outpatient department, or a hospital. Treatment generally begins at a hospital so that the doctor can observe the therapy's effects closely and make any adjustments that are needed. The duration of the combination therapy depends on the kind of biofilm being treated, the age and condition of the patient, the stage and type of the patient's biofilm infection, and how the patient's body responds to the treatment. Drug administration may be performed at different intervals (e.g., daily, weekly, or monthly) and the administration of each agent can be determined individually. Combination therapy may be given in on-and-off cycles that include rest periods so that the patient's body has a chance to build healthy new cells and regain its strength.

By "isolated polynucleotide" is meant a nucleic acid (e.g., a DNA) that is free of the genes which, in the naturally-occurring genome of the organism from which the nucleic acid molecule of the invention is derived, flank the gene. The term therefore includes, for example, a recombinant DNA that is incorporated into a vector; into an autonomously replicating plasmid or virus; or into the genomic DNA of a prokaryote or eukaryote; or that exists as a separate molecule (for example, a cDNA or a genomic or cDNA fragment produced by PCR or restriction endonuclease digestion) independent of other sequences. In addition, the term includes an RNA molecule which is transcribed from a DNA molecule, as well as a recombinant DNA which is part of a hybrid gene encoding additional polypeptide sequence.

By "polypeptide" is meant any chain of amino acids, regardless of length or post-translational modification (for example, glycosylation or phosphorylation).

By an "isolated polypeptide" is meant a polypeptide of the invention that has been separated from components which naturally accompany it. Typically, the polypeptide is isolated when it is at least 60%, by weight, free from the proteins and naturally-occurring organic molecules with which it is naturally associated. Preferably, the preparation is at least 75%, more preferably at least 90%, and most preferably at least 99%, by weight, a polypeptide of the invention. An isolated polypeptide of the invention may be obtained, for example, by extraction from a natural source (for example, a pathogen); by expression of a recombinant nucleic acid encoding such a polypeptide; or by chemically synthesizing the protein. Purity can be measured by any appropriate method, for example, column chromatography, polyacrylamide gel electrophoresis, or by HPLC analysis.

By "substantially identical" is meant a polypeptide or nucleic acid molecule (e.g., a polynucleotide) exhibiting at least 50% identity to a reference amino acid sequence (for example, any one of the amino acid sequences described herein) or nucleic acid sequence (for example, any one of the nucleic acid sequences described herein). Preferably, such a sequence is at least 60%, more preferably 80%, and most preferably 90% or even 95% identical at the amino acid level or nucleic acid to the sequence used for comparison.

Sequence identity is typically measured using sequence analysis software (for example, Sequence Analysis Software Package of the Genetics Computer Group, University of Wisconsin Biotechnology Center, 1710 University Avenue, Madison, WI 53705, BLAST, BESTFIT, GAP, or PILEUP/PRETTYBOX programs). Such software matches identical or similar sequences by assigning degrees of homology to various substitutions, deletions, and/or other modifications. Conservative substitutions typically include substitutions within the following groups: glycine, alanine; valine, isoleucine, leucine; aspartic acid, glutamic acid, asparagine, glutamine; serine, threonine; lysine, arginine; and phenylalanine, tyrosine. In an exemplary approach to determining the

degree of identity, a BLAST program may be used, with a probability score between e^{-3} and e^{-100} indicating a closely related sequence.

By "transformed cell" is meant a cell into which (or into an ancestor of which) has been introduced, by means of recombinant DNA techniques, a polynucleotide molecule encoding (as used herein) a polypeptide of the invention.

By "positioned for expression" is meant that the polynucleotide of the invention (e.g., a DNA molecule) is positioned adjacent to a DNA sequence which directs transcription and translation of the sequence (i.e., facilitates the production of, for example, a recombinant polypeptide of the invention, or an RNA molecule).

By "purified antibody" is meant an antibody which is at least 60%, by weight, free from proteins and naturally-occurring organic molecules with which it is naturally associated. Preferably, the preparation is at least 75%, more preferably 90%, and most preferably at least 99%, by weight, antibody. A purified antibody of the invention may be obtained, for example, by affinity chromatography using a recombinantly-produced polypeptide of the invention and standard techniques.

By "specifically binds" is meant a compound or antibody which recognizes and binds a polypeptide of the invention but which does not substantially recognize and bind other molecules in a sample, for example, a biological sample, which naturally includes a polypeptide of the invention.

By "derived from" is meant isolated from or having the sequence of a naturally-occurring sequence (e.g., a cDNA, genomic DNA, synthetic, or combination thereof).

By "inhibiting biofilm formation" is meant the ability of a candidate compound to decrease the development or progression of biofilm formation. Preferably, such inhibition decreases biofilm formation by at least 1% to 5%, more preferably by at least 10%, 15%, 20%, or 25%, and most preferably by at least 30% to 50%, as compared to biofilm formation in the absence of the candidate compound in any appropriate pathogenicity assay (for example, those assays described herein). In one particular example, inhibition is measured by continuous culture conditions of a microbe exposed to a candidate compound or extract, a decrease in the level of biofilm formation relative

to the level of biofilm formation of the microbe not exposed to the compound indicating compound-mediated inhibition of biofilm formation.

By "biofilm regulator polynucleotide" is meant a polynucleotide encoding a cellular component (e.g., PvrR) that modulates phenotypic switching, such as a phenotypic switch that occurs during biofilm formation, disintegration, or both.

By "phenotypic switching" is meant the reversible alteration of one or more phenotypic characteristics. Such an alteration typically occurs, for example, when a wild-type microbe develops into an antibiotic-resistant phenotypic variant or when an antibiotic-resistant phenotypic variant develops into a wild-type microbe.

By "immunological assay" is meant an assay that relies on an immunological reaction, for example, antibody binding to an antigen. Examples of immunological assays include ELISAs, Western blots, immunoprecipitations, and other assays known to the skilled artisan.

By a "two-component regulatory system" is meant a regulatory system that includes at least two components such as a sensor that senses an environmental signal and a response regulator that modulates one or more effectors.

By "aggregation" is meant a collection of two or more individual microorganisms into a mass or clump, such that the individuals form an aggregated microbial unit. Aggregation can be measured using assays provided herein. Examplary assays include visual inspection, measuring attachment to a surface, or by assaying for biofilm formation using methods known to the skilled artisan.

By "pathogenicity" is meant the ability of a microorganism to cause disease. A microorganism that forms a biofilm, has increased antibiotic resistance, or displays phenotypic variation is more pathogenic than a wild-type microorganism in that it is less susceptibile to conventional antibiotic treatment.

The invention provides a number of targets that are useful for the development of drugs that specifically block the biofilm formation of a microbe. In addition, the methods of the invention provide a facile means to identify compounds that are safe for use in eukaryotic host organisms (i.e., compounds which do not adversely affect the normal development and physiology of the organism), and efficacious against

pathogenic microbes (i.e., by suppressing the virulence of a pathogen). In addition, the methods of the invention provide a route for analyzing virtually any number of compounds for an anti-virulence effect with high-volume throughput, high sensitivity, and low complexity. The methods are also relatively inexpensive to perform and enable the analysis of small quantities of active substances found in either purified or crude extract form.

Other features and advantages of the invention will be apparent from the detailed description, and from the claims.

Brief Description of the Drawings

Figure 1A shows the reversion of PA14 rough small colony variants (RSCV) to the wild-type phenotype as observed at the edges of the colonies (arrow) after 2-3 days incubation on antibiotic free LB agar at room temperature.

Figure 1B shows a confocal scanning laser microscopic analysis of bacterial aggregates (arrows) formed by wild-type PA14 and PA14 RSCV expressing green fluorescent protein (GFP) after overnight growth in liquid broth. Scale bar, 25 μm.

Figure 1C shows the attachment of wild-type PA14 and antibiotic resistant variants to polyvinylchloride plastic (PVC) after 6 hours of growth.

Figure 1D shows a confocal laser scanning microscope analysis of biofilm formed by wild-type PA14 and PA14 RSCV expressing GFP in flow-chambers under continuous culture conditions. Scale bar, 50 μm.

Figure 1E shows PA14 and PA14 RSCV biofilm resistance to tobramycin as determined by measuring viable biomass on 45 hour-old established biofilms before (filled bars) and after (open bars) 36-hour tobramycin (200 μg/ml) treatment.

Figure 2A shows the effect of different environmental stimuli on the rate of appearance of antibiotic resistant variants. This was determined by growing the cultures of wild-type PA14 under the specified conditions on media containing 200 μg/ml kanamycin.

Figure 2B shows the minimal inhibitory concentrations of kanamycin for strain PA14 using the different conditions specified.

Figure 3A shows the reversion of PA14 RSCV present in sputum samples of a cystic fibrosis patient (designated "CF 5") as observed on the edges of the variant colonies (arrow) after prolonged incubation on antibiotic-free medium at room temperature.

Figure 3B shows the increased attachment to PVC plastic of antibiotic resistant variants SCV 42 and SCV 43 obtained after plating CF isolates CF 42 and CF 43 on tobramycin (10 μg/ml).

Figure 4A shows the attachment to PVC plastic of PA14, antibiotic resistant variants, and PA14 RSCV carrying pEd202 (PA14 RSCV /pED202) or pUCP19 (PA14 RSCV /pUCP19) after 4 hours of growth was quantitated.

Figure 4B shows the predicted amino acid sequence alignment of PvrR with the sequences that correspond to VieA from *V. Cholerae* and the *P. aeruginosa* PAO1 putative response regulator PA3947 (PAO1 RR). Numbers above the scale indicate number of amino acids. Lower panel contains domain family numbers according to ProDom nomenclature.

Figure 4C shows that the *pvrR* gene is flanked by two open reading frame regions (ORFs), designated *ORF1* and *ORF3*, with the same transcriptional orientation. Start codons within ORFs were assigned based on visual inspection for appropriately spaced ribosome-binding sequences.

Figure 4D shows the number of variants resistant to kanamycin (200 μg/ml). This was evaluated after plating overnight cultures of PA14 and PA14 overexpressing PvrR (PA14/pED202).

Figure 4E shows the attachment to PVC plastic of PA14 and PA14 overexpressing PvrR (PA14/pED202) after 12 hours of growth, quantitated as described herein.

Figure 4F shows the number of antibiotic resistant variants for PA14 and the *pvrR* mutant (*ΔpvrR)* as determined by plating overnight cultures on LB agar containing kanamycin (200 μg/ml).

Figure 5A shows the nucleic acid sequence of *pvrR* (SEQ ID NO:1).

Figure 5B shows the nucleic acid sequence of an *ORF1* polynucleotide (SEQ ID NO:3). This polynucleotide sequence begins at nucleotide 1504 and ends at nucleotide 2919 of SEQ ID NO: 7 as shown in Figure 5G.

Figure 5C shows the nucleic acid sequence of an ORF3 polynucleotide (SEQ ID NO:5). This polynucleotide sequence begins at nucleotide 4385 and ends at nucleotide 6379 of SEQ ID NO:7 as shown in Figure 5G.

Figure 5D shows the deduced amino acid sequence of PvrR (SEQ ID NO:2).

Figure 5E shows the deduced amino acid sequence of a polypeptide (SEQ ID NO:4) encoded by the polynucleotide shown in Figure 5B.

Figure 5F shows the deduced amino acid sequence of a polypeptide (SEQ ID NO:6) encoded by the polynucleotide shown in Figure 5C.

Figure 5G shows the nucleic acid sequence (SEQ ID NO:7) that includes the pvrR gene (SEQ ID NO:1), and the ORF1 (SEQ ID NOS:3 and 8-18) and ORF3 (SEQ ID NOS:5 and 30-34) regions. The start and stop codons for the identified open reading frames are highlighted.

Figures 6A-6K show the nucleotide sequences of several open reading frames identified in the ORF1 region (SEQ ID NO:8 begins at nucleotide 124 and ends at nucleotide 2919; SEQ ID NO:9 begins at nucleotide 199 and ends at nucleotide 2919; SEQ ID NO:10 begins at nucleotide 217 and ends at nucleotide 2919; SEQ ID NO:11 begins at nucleotide 256 and ends at nucleotide 2919; SEQ ID NO:12 begins at nucleotide 295 and ends at nucleotide 2919; SEQ ID NO:13 begins at nucleotide 307 and ends at nucleotide 2919; SEQ ID NO:14 begins at nucleotide 511 and ends at nucleotide 2919; SEQ ID NO:15 begins at nucleotide 760 and ends at nucleotide 2919; SEQ ID NO:16 begins at nucleotide 790 and ends at nucleotide 2919; SEQ ID NO:17 begins at nucleotide 919 and ends at nucleotide 2919; and SEQ ID NO18 begins at nucleotide 1429 and ends at nucleotide 2919).

Figures 6L-6V show the deduced amino acid sequences of the polypeptides (SEQ ID NOS: 19-29) identified in Figures 6A-6K above.

Figures 7A-7E show the nucleotide sequence of several open reading frames identified in the ORF3 region (SEQ ID NO:30 begins at nucleotide 4388 and ends at

nucleotide 6379; SEQ ID NO:31 begins at nucleotide 4550 and ends at nucleotide 6379; SEQ ID NO:32 begins at nucleotide 4572 and ends at nucleotide 6379; SEQ ID NO:33 begins at nucleotide 4880 and ends at nucleotide 6379;and SEQ ID NO:34 begins at nucleotide 5258 and ends at nucleotide 6379).

Figures 7F-7J show the deduced amino acid sequences of the polypeptides (SEQ ID NOS:35-39) identified in Figures 7A-7E above.

Detailed Description

Overview

Pseudomonas aeruginosa is the most important pathogen in the lungs of cystic fibrosis (CF) patients. Colonization of the CF lung by *P. aeruginosa* persists despite the use of long-term antibiotic therapy, since antibiotic treatment rarely results in eradication of the infection. Reports have suggested a direct link between resistance to antimicrobial compounds and the ability of *P. aeruginosa* to form biofilm in CF lungs. Other hypotheses explain *P. aeruginosa* antibiotic resistance by postulating that factors within the CF respiratory tract select for phenotypic variants suited to survive antimicrobial treatment. As is discussed below, we have determined that a clinical isolate of *P. aeruginosa*, strain PA14, was capable of growing under inhibitory concentrations of the antibiotic kanamycin (up to 40 times the susceptibility level of the strain) when bacteria had undergone phenotypic variation. The antibiotic resistant variant colonies obtained from kanamycin plates were smaller in size and had a different colony morphology compared to the wild-type. Analysis of the phenotype of PA14 RSCV indicated that these variants exhibited increased aggregation and attachment to glass tubes and polyvinylchloride plastic (PVC) as a result of enhanced surface hydrophobicity. Consistent with these observations, several PA14 RSCV clones were hyperpiliated when analysed by transmission electron microscopy. Moreover, examination of biofilms cultivated in flow chamber cells showed that PA14 RSCV formed more biofilm and faster than the wild-type strain. The biofilm formed by PA14 RSCV also showed increased resistance to tobramycin relative to wild-type PA14 biofilm. Similar results were obtained for several CF isolates using different antibiotics

(including tobramycin), suggesting that nonspecific antibiotic resistance acquired through phenotypic variation is a common mechanism in *P. aeruginosa*. Moreover, analysis of sputum samples taken from CF patients revealed that antibiotic treatment selects for antibiotic resistant variants. The frequency with which antibiotic resistant variants appeared was also affected by environmental stimuli. Environmental stimuli such as salt concentration, temperature, and bacterial media altered the frequency of appearance of resistant variants.

To identify components involved in the regulation of antibiotic resistance mediated by phenotypic variation, a library of PA14 chromosomal DNA was transferred into PA14 RSCV and screened for colonies displaying wild-type colony size and morphology. This led to the identification of a clone, pED202, that restored the colony, the autoagglutination, and attachment phenotypes of PA14 RSCV variants to wild-type. pED202 contained a single gene (designated *pvrR* for phenotype variant regulator) that showed sequence similarities to response regulator elements of the two-component regulatory system found in *Vibrio* cholerae response regulator VieA, and in *P. aeruginosa* strain PAO1 (ORF PA3947).

Consistent with the putative role of PvrR in the regulation of phenotypic switching, overexpression of PvrR from pED202 in wild-type PA14 resulted in reduced attachment to PVC plastic. Moreover, examination of the frequency of resistant variants obtained from kanamycin plates showed a reduction in the number of colonies resistant to antibiotic obtained from the PvrR overexpressing strain. An in-frame deletion of *pvrR* (Δ*pvrR*) constructed in PA14 increased frequency of appearance of resistant variants on kanamycin plates with respect to the wild-type, confirming the involvement of *pvrR* in the regulation of phenotypic switching. These results suggested that PvrR might be acting upstream of the switch, since inactivation of *pvrR* by mutation did not result in conversion to the variant type.

Below we describe the cloning and characterization of PvrR, a regulator of biofilm-mediated antibiotic resistance and a target for compounds useful in antibacterial therapy, along with antibiotics, for the treatment of chronic infections and biofilm control in medical and industrial settings. In addition, we describe the identification of

open reading frame regions, designated ORF1 and ORF3, that flank the pvrR gene. The following examples are for the purposes of illustrating the invention, and should not be construed as limiting.

Appearance of Rough Small Colony Variants with Increased Antibiotic Resistance

When cultured under high concentrations of antibiotic, *Pseudomonas aeruginosa* PA14 was found to shift its development to a rough small colony phenotype, leading to the production of antibiotic resistant colonies. To induce such phenotypic variants, an overnight culture of *P. aeruginosa* strain PA14 (UCBPP-PA14) was inoculated onto Luria-Bertani (LB) containing 200 μg/ml of kanamycin, incubated at 37°C for 48 hours, at which time, antibiotic resistant rough small variants were isolated. Antibiotic resistant colonies arose at a frequency of 10^{-6}-10^{-7}. The colonies identified on these plates were one-tenth the size of wild type and exhibited a rough phenotype compared to the smooth colony type of wild-type PA14. One class of kanamycin resistant variants (approximately 30%) exhibited a rough phenotype compared to the smooth colony type of wild-type PA14. When incubated for three to five days in LB media without antibiotic at room temperature, the rough phenotype reverted to the wild-type phenotype (Figure 1A), indicating that the phenotypic changes were transient, and not due to mutation. In addition to being resistant to kanamycin, (up to 40 times the susceptibility level of the wild-type), 8 individual PA14 RSCV colonies tested were also resistant to amikacin (30 μg/ml), carbenicillin (300 μg/ml), gentamicin (30 μg/ml), tobramycin (10 μg/ml), and tetracycline (150 μg/ml). Consistent with this latter result, antibiotic resistant variants were also obtained at frequencies of about 10^{-7} by plating overnight cultures of PA14 on media containing similar concentrations of the antibiotics mentioned above. Although RSCV colonies were smaller than wild-type, their small colony size was not a consequence of slow growth since the generation time of RSCV in liquid medium was not significantly different from that of the wild-type, even in LB containing 200 μg/ml kanamycin.

Phenotypic Changes Associated With Appearance of Resistance

To establish a connection between the phenotypic switch from wild-type to small variant colony and the emergence of antibiotic resistance, comparative attachment, agglutination, and biofilm formation studies of wild-type PA14 and PA14 RSCV were conducted.

The results of these experiments showed that PA14 RSCV formed visible bacterial aggregates when overnight liquid cultures were left without shaking at room temperature (Figure 1B). Moreover, abundant bacterial aggregates formed when liquid cultures were grown with gentle agitation, indicating that PA14 RSCV had increased cell-cell attachment compared to the wild-type phenotype.

In addition to the autoagglutination phenotype, PA14 RSCV developed a visible biofilm on the walls of glass tubes after overnight incubation in liquid culture. Wild-type PA14 failed to form a similar biofilm under these conditions. These results indicated that cell-surface interactions, as well as cell-cell interactions were increased in the variant. Consistent with this observation, PA14 RSCV were found to have increased attachment to PVC plastic (Figure 1C) in assays conducted in 96-well microtiter plates. When reversion was induced in PA14 RSCV, the reverted bacteria showed wild-type levels of both agglutination and attachment to glass and PVC plastic.

To quantitatively assess differences between the strains, standard bacterial attachment assays were performed in 96-well polyvinylchloride (PVC) plastic plates according to the methods described by O'Toole et al. (*Mol. Microbiol.* 30: 295, 1998). Overnight cultures of PA14 and PA14 RSCVwere diluted to an OD_{600} of 0.1 in fresh minimal M63 salts supplemented with glucose (0.3%), $MgSO_4$ (1 mM), and casamino acids (CAA, 0.5%). Aliquots of 100 µl were next dispensed into the wells of PVC plastic microtiter plates and incubated for 6 hours at 37°C. The attachment of bacteria to the walls of the microtiter well was then detected by staining with 1% crystal violet dissolved in water. Dye not associated with bacteria was removed by thorough rinsing with water. Bacteria-associated dye was solubilized using 95% ethanol and absorbance was determined at OD_{550}.

In addition, since the ability of bacteria to attach to each other and to surfaces depends in part on the interaction of hydrophobic domains (Drumm et al., *J. Clin. Invest.* 84:1588, 1989), the hydrophobic surface properties of the wild-type and PA14 RSCV were determined using a standard salt aggregation test (Sherman et al., *Infect. Immun.* 49:797, 1985). 5 x 10^8 bacteria per ml in 0.025 ml were mixed on a microscope slide with an equal volume of ammonium sulfate in 0.002 M sodium phosphate, pH 6.8. The ammonium sulfate concentrations varied from 0.0625 M to 4.0 M, and the presence of salt-induced bacterial aggregation was monitored for 2 minutes at room temperature by phase-contrast microscopy. Agglutination in salt concentrations of less than 0.1 M is taken as an indication of the presence of a hydrophobic bacterial surface. Hydrophilic surfaces were demonstrated by the agglutination of bacteria only in high salt concentrations (2.0 to 4.0 M).

The data obtained from the salt aggregation tests showed that PA14 RSCV were agglutinated at a lower salt concentration (0.125 M) compared to the wild-type PA14 (0.5 M), suggesting that PA14 RSCV has a higher degree of surface hydrophobicity than the wild-type. Therefore, the data indicated that a change in the hydrophobic properties of the surface of the bacteria was partially responsible for the general increase in surface attachment of the PA14 RSCV phenotypic variant. To further demonstrate the role of hydrophobicity in surface attachment, PA14 RSCV were cultured in the presence of tetramethyl urea (TMU), a hydrophobic bond-breaking agent, at a concentration of 200 mM. Addition of TMU to the culture media was found to reduce the attachment of the phenotypic variant PA14 RSCV to wild-type levels, confirming the hydrophobic nature of the bacterial surface. TMU, at the concentration used in these assays, did not affect cell viability.

Transmission electron microscopic analysis of several PA14 RSCV clones revealed that they were hyperpiliated, which is consistent with the increased hydrophobicity and agglutination phenotypes. However, the various phenotypes of PA14 RSCV were not simply a consequence of hyperpiliation since a hyperpiliated mutant of *P. aeruginosa* PA14, *pilU*, exhibited only marginally enhanced hydrophobicity and attachment to PVC plastic and did not exhibit enhanced resistance to

antibiotics (data not shown). These results are consistent with previous reports which indicated that phenotypic variation in Gram-negative bacteria involve changes in expression of a number of surface structures, outer membrane proteins, and lipopolysaccharides resulting in altered aggregation and colony morphology. Several PA14 RSCV clones were tested in the experiments described above and all exhibited similar phenotypes. A single PA14 RSCV clone was therefore chosen for further analysis.

To determine whether the antibiotic resistant phenotype of PA14 RSCV is associated with altered biofilm formation, PA14 RSCVwas cultured under biofilm-forming conditions as follows. For biofilm characterization, PA14 RSCV biofilms were cultivated under continuous culture conditions in flow-chambers with channel dimensions of 12 by 52 by 2 mm. Flow media consisted of M63 supplemented with 0.5% casamino acids and 0.3% glucose. For measurement of biofilm resistance, bacteria were cultivated in flow-chambers with channel dimensions of 1 by 40 by 4 mm (Stovall Inc., Greensboro, NC). In this case, flow media consisted of FAB medium (0.1 mM $CaCl_2$, 0.01 mM Fe-EDTA, 0.15 mM NH_4SO_4, 0.33 mM Na_2HPO_4, 0.2 mM KH_2PO_4 and 1 mM $MgCl_2$) supplemented with casamino acids (0.5%) and sodium citrate (10 mM). Flow-cells in both cases were inoculated with 100-fold dilutions of overnight cultures of PA14 and PA14 RSCV carrying the green fluorescent protein (GFP) in plasmid SMC21, a derivative of pSMC2 (Bloemberg et al., *Appl. Environ. Microbiol.* 63: 4543-4551, 1997). After inoculation, the medium flow was stopped for 1 hour. Medium flow was then resumed at a rate of 0.2 ml/min using a peristaltic pump (IsmaTec, Zurich, Switzerland), and the flow-cell system was incubated at 37° C. Analysis of biofilm spatial structures was performed using confocal scanning laser microscopy (CSLM) using a Leica TCS SP system (Leica Lasertechnik, GmgH, Heidelberg, Germany). Image analysis of antibiotic-treated biofilms was done in structures contained within serial section stacks of images delimited by freehand drawing. Pixel intensities unique to GFP-labeled bacteria and surrounding biofilm were established by the threshold limit technique. The volume (in μm^3) of individual biofilm

structures was determined from serial sections using ImageSpace software (Molecular Dynamics, Sunnyvale, CA).

The results from these studies showed that the PA14 RSCV phenotypic variant formed not only more biofilm than the wild-type strain, but also formed biofilm faster (RSCV microcolonies appeared 4-5 hours earlier than wild-type). Moreover, PA14 RSCV and wild-type PA14 displayed significantly different patterns of biofilm development. Wild-type PA14 initially formed regularly-spaced, flat, circular, microcolonies that eventually developed into ball-shaped microcolonies. In contrast, PA14 RSCV formed irregularly shaped three-dimensional structures that were densely packed with bacteria, without the typical microcolony morphology (Figure 1D). Finally, the biofilm structures formed by PA14 RSCV were larger in size than the wild-type microcolonies, and biofilms from PA14 RSCV contained more biomass than the wild-type.

To determine whether PA14 and PA14 RSCV biofilms exhibited antibiotic resistance that paralleled the resistance observed on plates containing antibiotic, established PA14 and PA14 RSCV biofilms grown in flow chambers were exposed to a continuous flow of tobramycin (200 μg/ml). Viable biomass was measured by CSLM analysis of GFP-tagged PA14 and PA14 RSCV cells using GFP expression as a viability marker as described previously (Figure 1E). Consistent with the results obtained in plates, the biofilm formed by PA14 RSCV was more resistant to tobramycin treatment than the wild-type PA14 biofilm.

Phenotypic variation is a common phenomenon in Gram-negative bacteria that often involves environmentally regulated changes in observable phenotypes produced by modifications in surface components. The effect that different environmental stimuli had on the appearance of kanamycin–resistant phenotypic variants was examined. Bacteria were grown in LB broth, or in supplemented LB with appropriate antibiotics at the indicated temperature with aeration. As shown in Figure 2A, a 40-fold increase in the frequency of appearance of resistant variants (not just PA14 RSCV) was observed on LB media supplemented with 85 mM NaCl as compared to the same medium without NaCl. Moreover, the frequency of variants increased 200-fold when plates were

incubated at 25°C compared to 37°C (Figure 2A). Finally, a dramatic 10^6 - fold increase was obtained on minimal M63 salts as compared to LB medium (Figure 2A). Minimal salt media consisted of M63 supplemented with 0.3% glucose, 1 mM $MgSO_4$, and 0.5% casamino acids. Importantly, there was a correlation between the frequency of appearance of kanamycin resistant variants on plates and minimal inhibitory concentrations (MICs) of kanamycin in liquid culture for the wild-type PA14 using the culture conditions described above (Figure 2B). For example, the high frequency of resistant variants obtained on M63 correlated with the relatively high concentration of kanamycin (475 μg/ml) required to inhibit the growth of PA14 in M63 liquid medium (Figures 2A and 2B). These data indicated that the components involved in the formation of antibiotic resistant variants are differentially regulated by environmental signals. Moreover, the data indicated that the portion of the population that becomes resistant to antibiotics through phenotypic variation was largely dependent on environmental conditions.

Small Colony Variants in CF Sputum Samples

The presence of phenotypic variants with small colony phenotypes has been reported in cystic fibrosis (CF) patients (Haussler et al., *Clin. Infect. Dis.* 29:621, 1999). Emergence of this and other variant phenotypes in the CF lung has also been linked to prolonged antibiotic treatment (McNamara et al., *Int. J. Antimicrob. Agents* 14:117, 2000; Kahl et al., *J. Infect. Dis.* 177:1023, 1998). To investigate whether antibiotic treatment in *P. aeruginosa* CF infections results in selection for resistant variants, we looked for the presence of small colony variants in CF sputum samples.

Five CF sputum samples from the Clinical Microbiology Laboratory at Massachusetts General Hospital were suspended in 5 ml of 10 mM $MgSO_4$. Serial dilutions of the samples were then plated onto cetrimide agar plates with and without antibiotics. The plates were screened for the presence of *P. aeruginosa* after 24 and 48 hours of incubation at 37°C. The identity of the colonies was later confirmed by probing colony lifts with the exotoxin A gene from *P. aeruginosa*. To this end, the *EcoRI-HindIII* fragment of plasmid pRGI containing the exoA gene (Samadpour et al., *J. Clin.*

Microbiol. 26:2319-23, 1988) was gel isolated and labeled using a random priming kit (Boehringer, Mannheim, Indianapolis, Ind.). Colonies were transferred to nylon membranes and hybridizations were performed according to the manufacturer's recommendations (NEN Research Products, Boston, MA). Identification of colonies carrying the exoA gene was then performed using a Phosphorimager (Amersham Pharmacia Biotech Inc., Piscataway, NJ).

Five sputum samples obtained from five CF patients were evaluated for the presence of small colony variant bacteria. Two out of five sputum samples obtained from CF patients (patients 5 and 38) contained 100% rough small colony variants (Table 1) that reverted to a wild-type colony morphology upon prolonged incubation on antibiotic-free medium (Figure 3A). Importantly, both samples 5 and 38 corresponded to patients that were undergoing antibiotic treatment at the time the samples were obtained (intravenous (IV) amikacin/ceftazidime for two days and oral (O) levofloxacin/inhaled (I) tobramycin for six weeks respectively Table 1).

TABLE 1

	Sample 5	Sample 38	Sample 41	Sample 42	Sample 43
Antibiotic treatment of CF patients	Amikacin(IV) Ceftazidime(IV)	Tobramycin (I) Levofloxacin(0)	none	none	none
Small Colony variants in sputum sample (%)	100	100	< 0.11	0.00	< 0.12
Variants resistant to amikacin (%)	100	100	15	5	0.2
Variants resistant to gentamicin (%)	100	100	10	6.6	0.5
Variants resistant to tetracycline (%)	30	32	0	0	Not done
Variants resistant to tobramycin (%)	50	100	0.10	0	0.5

Table 1 shows the presence of small colony *P. aeruginosa* variants in sputum samples from five CF patients. The presence of *P. aeruginosa* antibiotic resistant small colony variants was determined by plating CF sputum samples on cetrimide agar with and without the indicated antibiotics.

Moreover, there was 29% enrichment in small colony variants in samples taken on two consecutive days from the patient that was undergoing intravenous antibiotic treatment.

As shown in Table 1, 30-100% of the small colony variants present in samples 5 and 38 were resistant to four different antibiotics (amikacin, gentamicin, tetracycline, and tobramycin) at concentrations equal to or higher than the minimal bactericidal concentration (MBC) of their respective reverted colonies. The proportion of small colony variants present in the samples that showed resistance to amikacin, gentamicin, tetracycline, and tobramycin was analyzed by simultaneously plating the sputum samples in cetrimide agar with and without antibiotics. The data obtained were compared to MBCs of the reverted colonies for the antibiotics in which variants were obtained *In vitro* susceptibility (MBC) to the different antibiotics used during the assays was determined by a standard tube dilution procedure described by Bailey and Scott (*Diagnostic Microbiology*, 313-329, 1974).

Although the other three CF sputum samples (41, 42 and 43) appeared to contain either a small proportion or no detectable small colony variants when plated on antibiotic free media, they did contain a considerable number (0.5–15%) of antibiotic resistant variants (Table 1). This discrepancy was due to the fact that it took the small colony variants 36-40 hours to form visible colonies, at which time the fast growing wild-type bacteria present in the sputum samples had overgrown the antibiotic free plates. Resistant variants with small colony phenotypes obtained from plating CF isolates 42 and 43 on media containing tobramycin (a front-line antibiotic used for the treatment of *P. aeruginosa* infections) exhibited increased attachment to PVC plastic (Figure 3B).

Identification of the Phenotypic Variation Regulator Gene

Phenotypic variation is a common mechanism in Gram-negative bacteria, and involves changes in observable phenotypes produced by modifications in surface components such as fimbriae, flagella, outer membrane proteins, and lipopolysaccharides. In the mushroom pathogen *P. tolaasii*, Greewal et al. (*J. Bacteriol.* 177:4658, 1995) identified a two-component regulatory element responsible for the phenotypic switch from smooth to rough phenotype that involved changes in colony morphology and motility. Since the phenotype displayed by PA14 RSCV was transient and involved alterations in surface properties, we hypothesized that a regulatory component was also responsible for the phenotypic switch observed in PA14.

To identify this component, a genomic library of strain PA14 constructed in the cosmid vector pJSR1 (Rahme et al., *Science* 268:1899, 1995) was mobilized in masse into PA14 RSCV by triparental mating using helper strain pRK2013 (Figurski et al., *Proc. Natl. Acad. Sci.* USA 76:1648, 1979). The resulting transconjugants were screened visually for colonies showing wild-type size and morphology (smooth colony phenotype). Individual transconjugants that showed wild-type characteristics were used to isolate the corresponding cosmids which were then reintroduced into PA14 RSCV to confirm the reversion of the phenotype. Moreover, cosmid DNA from the transconjugants was digested to completion with the restriction enzymes *EcoRI, PstI,* and *HindIII* and separated by electrophoresis on a 0.7% agarose gel.

A total of 2,500 transconjugants were screened for colonies displaying wild-type PA14 colony size and morphology. Two transconjugants that showed wild-type phenotypes were isolated, indicating that the inserts contained in the cosmids were able to induce reversion from small colony variant to wild-type phenotype. Two cosmid clones were isolated and reintroduced in PA14 RSCV to test for restoration of wild-type phenotype, and both clones were found to be capable of greatly enhancing the rate of PA14 RSCV reversion to the wild-type phenotype. Restriction digest profiles obtained with *EcoRI, PstI,* and *HindIII* restriction enzymes showed the presence of a cosmid with the same insert in both cases, which was designated pED20. Although the PA14 RSCV phenotype was normally very stable in liquid culture (i.e., no wild-type revertants

observed when an overnight culture was plated on LB agar), the majority of the cells in a PA14 RSCV culture carrying pED20 formed wild-type colonies after overnight incubation.

Cosmid pED20 was then subcloned into the pUCP19 plasmid vector using a PstI restriction digest. The clones obtained after transformation in *E. coli* were used to isolate plasmid DNA that was subsequently introduced into PA14 RSCV by electroporation. The resulting clones were screened visually for colonies showing wild-type size and morphology. Subcloning of pED20 produced pED202, which contained a 3.5-kb fragment, that restored the colony phenotype of PA14 RSCV variant to wild-type. Clone pED202 restored attachment phenotypes (Figure 4A), as well as the colony morphology and autoagglutination phenotypes of PA14 RSCV variants to wild-type. The vector alone did not have any effect on the phenotypes analyzed.

DNA sequencing and sequence analysis of the pED202 insert was then performed. The DNA fragments used for sequencing were PCR amplified initially using primers M13 and M13 reverse from the pUCP19 plasmid. Primers were later synthesized based on the sequencing data obtained. Sequencing data were analyzed using the DNAStar software (DNASTAR Inc., Madison, WI) to predict the open reading frames present in the pED202 3.5 kb insert. Sequence information was also compared with the sequence databases at the National Center for Biotechnology Information as well as to the *P. aeruginosa* PAO1 sequence generated by the *P. aeruginosa* genome project (Cystic Fibrosis Foundation and PathoGenesis Corporation).

Analysis of the sequencing data obtained from clone pED202 showed that the clone contained only one intact open reading frame. The nucleotide and predicted amino acid sequences of the ORF (designated *pvrR* for phenotype variant regulator) contained in clone pED202 were compared to the GenBank databases, and showed sequence similarities to response regulator elements of the two-component regulatory system. The search revealed 30% identity and 45% similarity in a 376 amino acid overlap to the *Vibrio cholerae* response regulator VieA, which is induced during intestinal infection in mouse. In addition, the ORF on pED202 showed 29% identity and 45% similarity to a probable two-component response regulator identified in *P.*

aeruginosa strain PAO1 (ORF PA3947). Interestingly, the region of the PA14 genome containing *pvrR* is not present in the fully sequence *P. aeruginosa* strain PAO1.

A homology search against domain sequences in the ProDom database (ProDom web site; http://prodes.Toulouse.inra.fr/prodom) identified 4 regions with high-scoring segment pairs in PvrR (Figure 4B). All 4 domains are also present in VieA and the PA01 putative response regulator (Figure 4B). Moreover, these 4 domains exhibit high levels of amino acid sequence similarity (30%-60%; Figure 4B). Sequence analysis of the regions located upstream and downstream of *pvrR* revealed the presence of two additional ORFs (designated *ORF1* and *ORF3* respectively; Figure 4C) with sequence homology to two-component regulatory elements.

The protein encoded by ORF1 has homology to probable sensor/response regulator hybrids from *P. aeruginosa* (35% identity and 49% similarity to ORF. PA2824), to the sensor protein RcsC (capsular synthesis regulator component C) from *Salmonella enterica* subsp. *enterica* serovar Typhi (30% identity and 51% similarity) and to a two-component sensor regulator (PheN) that modulates phenotypic switching in *P. tolaasii,* (31% identity and 45% similarity). The protein encoded by ORF3 shows 42% identity and 60% similarity to the GacS sensor kinase from *P. fluorescens*, and 41% identity and 59% similarity to the two-component sensor regulator that modulates phenotypic switching in *P. tolaasii* (PheN).

Figure 5G shows a nucleic acid sequence (SEQ ID NO:7) including polynucleotides identified in the ORF1 region (SEQ ID NOS:3, and 8-18), *pvrR* (SEQ ID NO:1), polynucleotides identified in the ORF3 region (SEQ ID NOS:5, and 30-34), and the intergenic regions. The start and stop codons for each open reading frame are indicated by highlighting. Figures 5B and 6A-K show the nucleotide sequences of several open reading frames identified in the ORF1 region. The deduced amino acid sequence of these open reading frames are shown in Figures 5E (SEQ ID NO:4) and 6L-6V (SEQ ID NOS:19-29).

Additionally, Figure 5C shows the nucleic acid sequence (SEQ ID NO:5) of one of several open reading frames identified in the ORF3 region. The deduced amino acid sequence of the polypeptide encoded by this nucleotide sequence is shown in Figure 5F

(SEQ ID NO:6). Figures 7A-7E (SEQ ID NOS:30-34) show the nucleotide sequences of several additional open reading frames identified in the ORF3 region. The deduced amino acid sequence of the polypeptides encoded by these nucleotide sequences are shown in Figures 7F-7J.

To determine whether *pvrR* or a highly similar *pvrR* homolog was present in the other *P. aeruginosa* strains, PCR analysis of 14 *P. aeruginosa* strains was performed using *pvrR*-specific primers. The specificity of the PCR products obtained was subsequently confirmed by Southern blotting and hybridization with a *pvrR*-specific probe. Results showed that 7 out of 7 CF isolates, 2 out of 3 clinical isolates and 3 out of 4 standard *P. aeruginosa* laboratory strains contained the *pvrR* gene fragment or a highly similar fragment (data not shown).

PvrR Overexpression

Consistent with the putative role of *PvrR* in the regulation of phenotypic switching, overexpression of PvrR from pED202 resulted in a 6-fold reduction in the frequency of resistant variants obtained after plating overnight cultures on kanamycin (200 μg/ml) plates compared to wild-type (Figure 4D). Plasmid pED202, containing the pvrR gene was introduced into wild-type PA14 by electoroporation using standard methods. Frequency of appearance of kanamycin resistant variants and attachment to 96-well PVC plates was assayed as described above. Interestingly, the PvrR overexpressing strain also caused a 2.5-fold reduction in attachment to PVC plastic with respect to the strain carrying the vector alone (Figure 4E).

pvrR Deletion Analysis

Since PvrR is involved in the regulation of the phenotypic switch from wild-type to phenotypic variant, a mutation in *pvrR* would be expected to alter the proportion of resistant variants present in the PA14 population. To test this hypothesis, a 914 bp in-frame deletion within *pvrR* (denoted "Δ *pvrR*") was generated by replacing 2.33 kb of the wild-type sequence of the *pvrR* gene with a 1.416 kb fragment amplified by PCR. The PCR-amplified DNA fragment was subcloned into the *Xba*I and *Sma*I restriction

sites of the positive selection suicide vector pCVD442 to generate pED167. Plasmid pED167 was then used in an allelic exchange procedure to introduce the fragment containing the deleted copy of *pvrR* into the homologous region of the PA14 chromosome, creating strain ED78. The deletion was confirmed by sequencing a PCR fragment containing *pvrR*.

This deletion of *pvrR* (Δ*pvrR*) in PA14 resulted in an increased frequency of appearance of resistant variants on kanamycin plates with respect to the wild-type (Figure 4F), confirming the involvement of *pvrR* in the regulation of phenotypic switching. The observation that 100% of the variants expressing wild-type *pvrR* reverted to the wild-type phenotype implicates PvrR is inducing reversion from variant to wild-type phenotypes. These results indicated that PvrR may be acting upstream of the switch, since inactivation of *pvrR* by mutation was not found to result in conversion to the variant type.

Isolation of Additional Biofilm Regulator Genes

Based on the nucleotide and amino acid sequences described herein, the isolation and identification of additional coding sequences of genes regulating the formation of microbial biofilm is made possible using standard strategies and techniques that are well known in the art. For example, any microbe that possesses the ability to form a biofilm can serve as the nucleic acid source for the molecular cloning of such a gene, and these sequences are identified as ones encoding a protein exhibiting structures, properties, or activities associated with biofilm formation, such as the PvrR (Figure 5D, SEQ ID NO:2), or any of the polynucleotides identified in the ORF1 (SEQ ID NOS:3 and 8-18) and ORF3 (SEQ ID NOS:5 and 30-34) regions.

In one particular example of such an isolation technique, any one of the nucleotide sequences described herein, including *pvrR* (Figure 5A, SEQ ID NO:1), *ORF1* (Figure 5B, SEQ ID NO:3), or *ORF3* (Figure 5C, SEQ ID NO:5) may be used, together with conventional methods of nucleic acid hybridization screening. Such hybridization techniques and screening procedures are well known to those skilled in the art and are described, for example, in Benton and Davis (*Science* 196:180, 1977);

Grunstein and Hogness (*Proc. Natl. Acad. Sci.*, USA 72:3961, 1975); Ausubel et al. (*Current Protocols in Molecular Biology*, Wiley Interscience, New York, 2001); Berger and Kimmel (*Guide to Molecular Cloning Techniques*, 1987, Academic Press, New York); and Sambrook et al., *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratory Press, New York. In one particular example, all or part of the *pvrR*, *ORF1*, or *ORF3* sequences (described herein) may be used as a probe to screen a recombinant DNA library for genes having sequence identity to the *pvrR*, *ORF1*, or *ORF3* genes. Hybridizing sequences are detected by plaque or colony hybridization according to standard methods.

Alternatively, using all or a portion of the amino acid sequences of PvrR, ORF1, or ORF3, one may readily design *pvrR*, *ORF1*, *or ORF3* gene-specific oligonucleotide probes, including degenerate oligonucleotide probes (i.e., a mixture of all possible coding sequences for a given amino acid sequence). These oligonucleotides may be based upon the sequence of either DNA strand and any appropriate portion of the *pvrR*, *ORF1*, *or ORF3* sequences. General methods for designing and preparing such probes are provided, for example, in Ausubel et al. (supra), and Berger and Kimmel, *Guide to Molecular Cloning Techniques*, 1987, Academic Press, New York. These oligonucleotides are useful for *pvrR*, *ORF1*, or *ORF3* gene isolation, either through their use as probes capable of hybridizing to *pvrR*, *ORF1*, or *ORF3* complementary sequences or as primers for various amplification techniques, for example, polymerase chain reaction (PCR) cloning strategies. If desired, a combination of different, detectably-labelled oligonucleotide probes may be used for the screening of a recombinant DNA library. Such libraries are prepared according to methods well known in the art, for example, as described in Ausubel et al. (supra), or they may be obtained from commercial sources.

As discussed above, sequence-specific oligonucleotides may also be used as primers in amplification cloning strategies, for example, using PCR. PCR methods are well known in the art and are described, for example, in *PCR Technology*, Erlich, ed., Stockton Press, London, 1989; *PCR Protocols: A Guide to Methods and Applications*, Innis et al., eds., Academic Press, Inc., New York, 1990; and Ausubel et al. (supra).

Primers are optionally designed to allow cloning of the amplified product into a suitable vector, for example, by including appropriate restriction sites at the 5' and 3' ends of the amplified fragment (as described herein). If desired, nucleotide sequences may be isolated using the PCR "RACE" technique, or Rapid Amplification of cDNA Ends (see, e.g., Innis et al. (supra)). By this method, oligonucleotide primers based on a desired sequence are oriented in the 3' and 5' directions and are used to generate overlapping PCR fragments. These overlapping 3'- and 5'-end RACE products are combined to produce an intact full-length cDNA. This method is described in Innis et al. (supra); and Frohman et al., *Proc. Natl. Acad. Sci.* USA 85:8998, 1988.

Partial sequences, e.g., sequence tags, are also useful as hybridization probes for identifying full-length sequences, as well as for screening databases for identifying previously unidentified related virulence genes.

In general, the invention includes any nucleic acid sequence which may be isolated as described herein or which is readily isolated by homology screening or PCR amplification using any of the nucleic acid sequences disclosed herein such as those shown in Figures 5A, 5C, 5G, 6A-K, or 7A-7E.

It will be appreciated by those skilled in the art that as a result of the degeneracy of the genetic code, a multitude of polynucleotide sequences encoding PvrR, ORF1, or ORF3, some bearing minimal similarity to the polynucleotide sequences of any known and naturally occurring gene, may be produced. Thus, the invention contemplates each and every possible variation of polynucleotide sequence that could be made by selecting combinations based on possible codon choices. These combinations are made in accordance with the standard triplet genetic code as applied to the polynucleotide sequence of naturally-occurring *pvrR, ORF1, or ORF3*, and all such variations are to be considered as being specifically disclosed.

Although nucleotide sequences which encode PvrR, ORF1, ORF3, or their variants are preferably capable of hybridizing to the nucleotide sequence of the naturally-occurring *pvrR, ORF1,* or *ORF3* under appropriately selected conditions of stringency, it may be advantageous to produce nucleotide sequences encoding PvrR, ORF1, ORF3, or their derivatives possessing a substantially different codon usage, e.g.,

inclusion of non-naturally occurring codons. Codons may be selected to increase the rate at which expression of the peptide occurs in a particular prokaryotic or eukaryotic host in accordance with the frequency with which particular codons are utilized by the host. Other reasons for substantially altering the nucleotide sequence encoding PvrR, ORF1, ORF3, and their derivatives without altering the encoded amino acid sequences include the production of RNA transcripts having more desirable properties, such as a greater half-life, than transcripts produced from the naturally occurring sequence.

The invention also encompasses production of DNA sequences which encode PvrR, ORF1, ORF3, or fragments thereof generated entirely by synthetic chemistry. After production, the synthetic sequence may be inserted into any of the many available expression vectors and cell systems using reagents well known in the art. Moreover, synthetic chemistry may be used to introduce mutations into a sequence encoding any one of PvrR, ORF1, ORF3, or any fragment thereof.

Also encompassed by the invention are polynucleotide sequences that are capable of hybridizing to the claimed polynucleotide sequences, and, in particular, to those shown in Figure 5A, 5B, 5C, 5G, 6A-6K, or 7A-7E and fragments thereof under various conditions of stringency. (See, e.g., Wahl, G. M. and S. L. Berger (1987) *Methods Enzymol.* 152:399; Kimmel, A. R. (1987) *Methods Enzymol.* 152:507) For example, stringent salt concentration will ordinarily be less than about 750 mM NaCl and 75 mM trisodium citrate, preferably less than about 500 mM NaCl and 50 mM trisodium citrate, and most preferably less than about 250 mM NaCl and 25 mM trisodium citrate. Low stringency hybridization can be obtained in the absence of organic solvent, e.g., formamide, while high stringency hybridization can be obtained in the presence of at least about 35% formamide, and most preferably at least about 50% formamide. Stringent temperature conditions will ordinarily include temperatures of at least about 30 °C, more preferably of at least about 37 °C, and most preferably of at least about 42 °C. Varying additional parameters, such as hybridization time, the concentration of detergent, e.g., sodium dodecyl sulfate (SDS), and the inclusion or exclusion of carrier DNA, are well known to those skilled in the art. Various levels of stringency are accomplished by combining these various conditions as needed. In a

preferred embodiment, hybridization will occur at 30 °C in 750 mM NaCl, 75 mM trisodium citrate, and 1% SDS. In a more preferred embodiment, hybridization will occur at 37 °C in 500 mM NaCl, 50 mM trisodium citrate, 1% SDS, 35% formamide, and 100 μg/ml denatured salmon sperm DNA (ssDNA). In a most preferred embodiment, hybridization will occur at 42 °C in 250 mM NaCl, 25 mM trisodium citrate, 1% SDS, 50% formamide, and 200 μg/ml ssDNA. Useful variations on these conditions will be readily apparent to those skilled in the art.

The washing steps which follow hybridization can also vary in stringency. Wash stringency conditions can be defined by salt concentration and by temperature. As above, wash stringency can be increased by decreasing salt concentration or by increasing temperature. For example, stringent salt concentration for the wash steps will preferably be less than about 30 mM NaCl and 3 mM trisodium citrate, and most preferably less than about 15 mM NaCl and 1.5 mM trisodium citrate. Stringent temperature conditions for the wash steps will ordinarily include temperature of at least about 25 °C, more preferably of at least about 42 °C, and most preferably of at least about 68 °C. In a preferred embodiment, wash steps will occur at 25°C in 30 mM NaCl, 3 mM trisodium citrate, and 0.1% SDS. In a more preferred embodiment, wash steps will occur at 42°C in 15 mM NaCl, 1.5 mM trisodium citrate, and 0.1% SDS. In a most preferred embodiment, wash steps will occur at 68°C in 15 mM NaCl, 1.5 mM trisodium citrate, and 0.1% SDS. Additional variations on these conditions will be readily apparent to those skilled in the art.

Methods for DNA sequencing are well known in the art and may be used to practice any of the embodiments of the invention. The resulting sequences are analyzed using a variety of algorithms which are well known in the art. (See, e.g., Ausubel, F. M. (1997) *Short Protocols in Molecular Biology*, John Wiley & Sons, New York N.Y., unit 7.7)

Polypeptide Expression

In general, polypeptides of the invention (e.g., PvrR, ORF1, or ORF3 as shown in Figures 5D, 5E, 5F, 6L-6V, or 7F-7J) may be produced by transformation of a

suitable host cell with all or part of a polypeptide-encoding nucleic acid molecule or fragment thereof in a suitable expression vehicle.

Those skilled in the field of molecular biology will understand that any of a wide variety of expression systems may be used to provide the recombinant protein. The precise host cell used is not critical to the invention. A polypeptide of the invention may be produced in a prokaryotic host (e.g., *E. coli*) or in a eukaryotic host (e.g., *Saccharomyces cerevisiae*, insect cells, e.g., Sf21 cells, or mammalian cells, e.g., NIH 3T3, HeLa, or preferably COS cells). Such cells are available from a wide range of sources (e.g., the American Type Culture Collection, Rockland, MD; also, see, e.g., Ausubel et al., supra). The method of transformation or transfection and the choice of expression vehicle will depend on the host system selected. Transformation and transfection methods are described, e.g., in Ausubel et al. (supra); expression vehicles may be chosen from those provided, e.g., in Cloning Vectors: A Laboratory Manual (P.H. Pouwels et al., 1985, Supp. 1987).

One particular bacterial expression system for polypeptide production is the *E. coli* pET expression system (Novagen, Inc., Madison, WI). According to this expression system, DNA encoding a polypeptide is inserted into a pET vector in an orientation designed to allow expression. Since the gene encoding such a polypeptide is under the control of the T7 regulatory signals, expression of the polypeptide is achieved by inducing the expression of T7 RNA polymerase in the host cell. This is typically achieved using host strains which express T7 RNA polymerase in response to IPTG induction. Once produced, recombinant polypeptide is then isolated according to standard methods known in the art, for example, those described herein.

Another bacterial expression system for polypeptide production is the pGEX expression system (Pharmacia). This system employs a GST gene fusion system which is designed for high-level expression of genes or gene fragments as fusion proteins with rapid purification and recovery of functional gene products. The protein of interest is fused to the carboxyl terminus of the glutathione S-transferase protein from *Schistosoma japonicum* and is readily purified from bacterial lysates by affinity chromatography using Glutathione Sepharose 4B. Fusion proteins can be recovered under mild

conditions by elution with glutathione. Cleavage of the glutathione S-transferase domain from the fusion protein is facilitated by the presence of recognition sites for site-specific proteases upstream of this domain. For example, proteins expressed in pGEX-2T plasmids may be cleaved with thrombin; those expressed in pGEX-3X may be cleaved with factor Xa.

Once the recombinant polypeptide of the invention is expressed, it is isolated, e.g., using affinity chromatography. In one example, an antibody (e.g., produced as described herein) raised against a polypeptide of the invention may be attached to a column and used to isolate the recombinant polypeptide. Lysis and fractionation of polypeptide-harboring cells prior to affinity chromatography may be performed by standard methods (see, e.g., Ausubel et al., supra).

Once isolated, the recombinant protein can, if desired, be further purified, e.g., by high performance liquid chromatography (see, e.g., Fisher, *Laboratory Techniques In Biochemistry And Molecular Biology*, eds., Work and Burdon, Elsevier, 1980).

Polypeptides of the invention, particularly short peptide fragments, can also be produced by chemical synthesis (e.g., by the methods described in *Solid Phase Peptide Synthesis*, 2nd ed., 1984 The Pierce Chemical Co., Rockford, IL). Also included in the invention are polypeptides which are modified in ways which do not abolish their pathogenic activity (assayed, for example as described herein). Such changes may include certain mutations, deletions, insertions, or post-translational modifications, or may involve the inclusion of any of the polypeptides of the invention as one component of a larger fusion protein.

The invention further includes analogs of any naturally-occurring polypeptide of the invention. Analogs can differ from the naturally-occurring the polypeptide of the invention by amino acid sequence differences, by post-translational modifications, or by both. Analogs of the invention will generally exhibit at least 85%, more preferably 90%, and most preferably 95% or even 99% identity with all or part of a naturally-occurring amino acid sequence of the invention. The length of sequence comparison is at least 15 amino acid residues, preferably at least 25 amino acid residues, and more preferably more than 35 amino acid residues. Again, in an exemplary approach to determining the

degree of identity, a BLAST program may be used, with a probability score between e^{-3} and e^{-100} indicating a closely related sequence. Modifications include in vivo and in vitro chemical derivatization of polypeptides, e.g., acetylation, carboxylation, phosphorylation, or glycosylation; such modifications may occur during polypeptide synthesis or processing or following treatment with isolated modifying enzymes. Analogs can also differ from the naturally-occurring polypeptides of the invention by alterations in primary sequence. These include genetic variants, both natural and induced (for example, resulting from random mutagenesis by irradiation or exposure to ethanemethylsulfate or by site-specific mutagenesis as described in Sambrook, Fritsch and Maniatis, *Molecular Cloning: A Laboratory Manual* (2d ed.), CSH Press, 1989, or Ausubel et al., supra). Also included are cyclized peptides, molecules, and analogs which contain residues other than L-amino acids, e.g., D-amino acids or non-naturally occurring or synthetic amino acids, e.g., β or γ amino acids.

In addition to full-length polypeptides, the invention also includes fragments of any one of the polypeptides of the invention. As used herein, the term "fragment," means at least 5, preferably at least 20 contiguous amino acids, preferably at least 30 contiguous amino acids, more preferably at least 50 contiguous amino acids, and most preferably at least 60 to 80 or more contiguous amino acids. Fragments of the invention can be generated by methods known to those skilled in the art or may result from normal protein processing (e.g., removal of amino acids from the nascent polypeptide that are not required for biological activity or removal of amino acids by alternative mRNA splicing or alternative protein processing events). The aforementioned general techniques of polypeptide expression and purification can also be used to produce and isolate useful peptide fragments or analogs (described herein).

Antibodies

The polypeptides disclosed herein or variants thereof or cells expressing them can be used as an immunogen to produce antibodies immunospecific for such polypeptides. "Antibodies" as used herein include monoclonal and polyclonal antibodies, chimeric, single chain, simianized antibodies and humanized antibodies, as

well as Fab fragments, including the products of an Fab immunolglobulin expression library.

To generate antibodies, a coding sequence for a polypeptide of the invention may be expressed as a C-terminal fusion with glutathione S-transferase (GST) (Smith et al., *Gene* 67:31, 1988). The fusion protein is purified on glutathione-Sepharose beads, eluted with glutathione, cleaved with thrombin (at the engineered cleavage site), and purified to the degree necessary for immunization of rabbits. Primary immunizations are carried out with Freund's complete adjuvant and subsequent immunizations with Freund's incomplete adjuvant. Antibody titres are monitored by Western blot and immunoprecipitation analyses using the thrombin-cleaved protein fragment of the GST fusion protein. Immune sera are affinity purified using CNBr-Sepharose-coupled protein. Antiserum specificity is determined using a panel of unrelated GST proteins.

As an alternate or adjunct immunogen to GST fusion proteins, peptides corresponding to relatively unique immunogenic regions of a polypeptide of the invention may be generated and coupled to keyhole limpet hemocyanin (KLH) through an introduced C-terminal lysine. Antiserum to each of these peptides is similarly affinity purified on peptides conjugated to BSA, and specificity tested in ELISA and Western blots using peptide conjugates, and by Western blot and immunoprecipitation using the polypeptide expressed as a GST fusion protein.

Alternatively, monoclonal antibodies which specifically bind any one of the polypeptides of the invention are prepared according to standard hybridoma technology (see, e.g., Kohler et al., *Nature* 256:495, 1975; Kohler et al., *Eur. J. Immunol.* 6:511, 1976; Kohler et al., *Eur. J. Immunol.* 6:292, 1976; Hammerling et al., In *Monoclonal Antibodies and T Cell Hybridomas*, Elsevier, NY, 1981; Ausubel et al., supra). Once produced, monoclonal antibodies are also tested for specific recognition by Western blot or immunoprecipitation analysis (by the methods described in Ausubel et al., supra). Antibodies which specifically recognize the polypeptide of the invention are considered to be useful in the invention; such antibodies may be used, e.g., in an immunoassay. Alternatively monoclonal antibodies may be prepared using the polypeptide of the

invention described above and a phage display library (Vaughan et al., *Nature Biotech* 14:309, 1996).

Preferably, antibodies of the invention are produced using fragments of the polypeptides disclosed herein which lie outside generally conserved regions and appear likely to be antigenic, by criteria such as high frequency of charged residues. In one specific example, such fragments are generated by standard techniques of PCR and cloned into the pGEX expression vector (Ausubel et al., supra). Fusion proteins are expressed in E. coli and purified using a glutathione agarose affinity matrix as described in Ausubel et al. (supra). To attempt to minimize the potential problems of low affinity or specificity of antisera, two or three such fusions are generated for each protein, and each fusion is injected into at least two rabbits. Antisera are raised by injections in a series, preferably including at least three booster injections.

Antibodies against any of the polypeptides described herein may be employed to treat bacterial infections, for example, those infections involving biofilm formation. Thus, among others, antibodies against, for example, polypeptides of PvrR (SEQ ID NO: 2), ORF1 (SEQ ID NO: 4), or ORF3 (SEQ ID NO: 6) shown respectively in Figures 5D, E, or F may be employed to treat infections, particularly bacterial infections and especially chronic infections associated with CF or biofilm formation associated with indwelling medical devices, conjunctivitis, pneumonia, and bacteremia.

Diagnostics

In another embodiment, antibodies which specifically bind any of the polypeptides described herein may be used for the diagnosis of bacterial infection. A variety of protocols for measuring such polypeptides, including ELISAs, RIAs, and FACS, are known in the art and provide a basis for diagnosing bacterial infections.

In another aspect, hybridization with PCR probes which are capable of detecting polynucleotide sequences, including genomic sequences, encoding *pvrR*, *ORF1*, *ORF3*, or closely related molecules may be used to identify nucleic acid sequences which encode its gene product. The specificity of the probe, whether it is made from a highly specific region, e.g., the 5' regulatory region, or from a less specific region, e.g., a

conserved motif, and the stringency of the hybridization or amplification (maximal, high, intermediate, or low), will determine whether the probe identifies only naturally occurring sequences encoding PvrR, ORF1, or ORF3 allelic variants, or related sequences.

In further embodiments, oligonucleotides or longer fragments derived from any of the polynucleotide sequences described herein may be used as targets in a microarray. The microarray can be used to monitor the expression level of large numbers of genes simultaneously and to identify genetic variants, mutations, and polymorphisms. This information may be used to determine gene function, to understand the genetic basis of a disorder, to diagnose a disorder, and to develop and monitor the activities of therapeutic agents. Microarrays may be prepared, used, and analyzed using methods known in the art. (See, e.g., Brennan et al., U.S. Pat. No. 5,474,796; Schena et al., *Proc. Natl. Acad. Sci.* 93:10614, 1996; Baldeschweiler et al., PCT application WO95/251116, 1995; Shalon, D. et al., PCT application WO95/35505, 1995; Heller et al., *Proc. Natl. Acad. Sci.* 94:2150, 1997; and Heller et al., U.S. Pat. No. 5,605,662.)

Screening Assays

As discussed above, we have identified a biofilm regulator gene, *pvrR*, of *P. aeruginosa* that mediates biofilm formation and antibiotic resistance by a microbe. Based on this discovery, we have developed screening assays for identifying compounds that enhance or inhibit the action of a polypeptide or the expression of a nucleic acid sequence of the invention. The method of screening may involve high-throughput techniques.

Any number of methods are available for carrying out such screening assays. In one working example, candidate compounds are added at varying concentrations to the culture medium of pathogenic cells expressing one of the nucleic acid sequences of the invention. Gene expression is then measured, for example, by standard Northern blot analysis (Ausubel et al., supra) or RT-PCR, using any appropriate fragment prepared from the nucleic acid molecule as a hybridization probe. The level of gene expression in the presence of the candidate compound is compared to the level measured in a control

culture medium lacking the candidate molecule. A compound which promotes an increase in the expression of the *pvrR* gene or functional equivalent is considered useful in the invention; such a molecule may be used, for example, as a therapeutic to combat the pathogenicity of an infectious organism, for example, by decreasing its ability to form a biofilm and rendering it susceptible to antibiotic treatment.

In another working example, the effect of candidate compounds may be measured at the level of polypeptide production using the same general approach and standard immunological techniques, such as Western blotting or immunoprecipitation with an antibody specific for a biofilm regulator polypeptide, such as PvrR. For example, immunoassays may be used to detect or monitor the expression of at least one of the polypeptides of the invention in a microbial organism. Polyclonal or monoclonal antibodies (produced as described above) which are capable of binding to such a polypeptide may be used in any standard immunoassay format (e.g., ELISA, Western blot, or RIA assay) to measure the level of the polypeptide. A compound which promotes an increase in the expression of the polypeptide is considered particularly useful. Again, such a molecule may be used, for example, as a therapeutic to combat the biofilm formation of an organism as is described above.

In yet another working example, candidate compounds may be screened for those which specifically bind to and agonize a PvrR polypeptide (a polypeptide having the amino acid sequences shown in Figure 5D) of the invention. The efficacy of such a candidate compound is dependent upon its ability to interact with the PvrR polypeptide or functional equivalent thereof. Such an interaction can be readily assayed using any number of standard binding techniques and functional assays (e.g., those described in Ausubel et al., supra). For example, a candidate compound may be tested *in vitro* for interaction and binding with a polypeptide of the invention and its ability to modulate biofilm formation may be assayed by any standard assay (e.g., those described herein).

In one particular working example, a candidate compound that binds to a polypeptide (e.g, PvrR) may be identified using a chromatography-based technique. For example, a recombinant polypeptide of the invention may be purified by standard techniques from cells engineered to express the polypeptide (e.g., those described above)

and may be immobilized on a column. A solution of candidate compounds is then passed through the column, and a compound specific for the pathogenicity polypeptide (e.g, biofilm regulator polypeptide) is identified on the basis of its ability to bind to the pathogenicity polypeptide (e.g, biofilm regulator polypeptide) and be immobilized on the column. To isolate the compound, the column is washed to remove non-specifically bound molecules, and the compound of interest is then released from the column and collected. Compounds isolated by this method (or any other appropriate method) may, if desired, be further purified (e.g., by high performance liquid chromatography). In addition, these candidate compounds may be tested for their ability to render a pathogen incapable of forming a biofilm (e.g., as described herein). Compounds isolated by this approach may also be used, for example, as therapeutics to treat or prevent the onset of a pathogenic infection, disease, or both. Compounds which are identified as binding to pathogenicity polypeptides (e.g, biofilm regulator polypeptides) with an affinity constant less than or equal to 10 mM are considered particularly useful in the invention.

Potential agonists include organic molecules, peptides, peptide mimetics, polypeptides, and antibodies that bind to a nucleic acid sequence or polypeptide of the invention (e.g, biofilm regulator polypeptides) and thereby increase its activity. Potential agonists also include small molecules that bind to and occupy the binding site of the polypeptide thereby preventing binding to cellular binding molecules, such that normal biological activity is prevented.

Compounds that decrease only antibiotic resistance of a microbe are also identified by monitoring reversion of bacterial colonies from the antibiotic resistant phenotype to the wild-type susceptible phenotype. In one working example, screens for compounds that increase reversion rate are conducted by plating antibiotic resistant variant bacteria on antibiotic-free media in the presence or absence of a candidate compound. The plates are then cultured using standard methods. The plates are then visually inspected for revertants, i.e., bacterial colonies having a wild-type phenotype. The number of wild-type phenotype bacterial colonies is compared between plates cultured in the presence or absence of a candidate compound. Compounds that increase

the number of wild-type revertants, relative to the number of wild-type revertants on a control plate without the compound, are taken as useful in the invention.

Additionally, compounds that decrease antibiotic resistance are identified by monitoring for an increase in the susceptibility of bacteria to antibiotics. In yet another working example, compounds that decrease antibiotic resistance are identified by plating wild-type bacteria on antibiotic containing plates in the presence or absence of a candidate compound. The plates are cultured using standard methods, and then visually inspected for bacterial colonies. The number of antibiotic resistant bacterial colonies is compared between plates cultured in the presence or absence of a candidate compound. Compounds that decrease the number of antibiotic resistant variant colonies, relative to the number of antibiotic resistant variant colonies on a control plate without the compound, are taken as useful in the invention.

In another working example, a gene that regulates biofilm formation is identified by monitoring its activity or activity of its encoded polypeptide, when mutated. Bacteria are mutagenized using standard methods, such as transposon mutagenesis. Mutagenized and wild-type bacteria are then plated on antibiotic containing plates. These plates are cultured using standard methods, and then are visually inspected for the presence of antibiotic resistant variant bacteria. The number of antibiotic resistant variant bacterial colonies (e.g., small colony variants) is compared between mutagenized bacterial plates and wild-type control plates. This comparison is typically conducted when variant colonies begin to appear on the wild-type plate. A decrease or increase in the number of antibiotic resistant variant bacterial colonies (e.g., small colony variants) on a plate containing mutagenized bacteria is taken as an indication of the presence of a genetic mutation in a gene that regulates biofilm formation. The mutated gene is then identified according to standard methods.

In yet another working example, a gene that regulates biofilm or phenotype-mediated antibiotic resistance is identified as follows. For example, a candidate gene (e.g., as part of a genomic library) is introduced into a variant host cell (e.g., *Pseudomonas aeruginosa* PA14 RSCV). Next, the transformed host cell is monitored for reversion from the rough small colony variant phenotype to wild-type. The plates

are then cultured using standard methods and monitored for the appearance of colonies with a wild-type phenotype. The number of wild-type phenotype bacterial colonies is then compared between plates containing transformants and variants carrying the vector alone. An increase in the number of wild-type revertants, relative to the number of wild-type revertants on a control plate with the vector alone, identifies a gene that regulates biofilm formation or phenotype-mediated antibiotic resistance. A gene identified using this method is subsequently isolated using standard procedures known in the art.

In another working example, small colony phenotypic variants are plated on an appropriate antibiotic medium (for example, those described herein) in the presence of a candidate compound and reversion to wild-type is monitored. Compounds that promote reversion from PA14 RSCV to wild-type are taken as being useful in the invention.

In another working example, a gene that regulates or is involved in phenotype-mediated or biofilm-mediated antibiotic resistance or biofilm formation is identified as follows. Bacteria are mutagenized using standard methods, such as transposon mutagenesis. Mutagenized bacteria are then plated on Trypticase Soy Agar (TSA) plates containing antibiotic. These plates are cultured using standard methods, and then inspected for bacterial growth. A decrease in the number of bacterial colonies or their absence on a mutagenized plate, relative to a control plate containing non-mutagenized bacteria identifies the presence of a genetic mutation in a gene that regulates phenotype-mediated or biofilm-mediated antibiotic resistance and biofilm formation. A gene identified using this method is subsequently isolated using standard procedures known in the art.

In another working example, a gene that regulates or is involved in phenotype-mediated or biofilm-mediated antibiotic resistance or biofilm formation is identified as follows. Bacteria are mutagenized using standard methods, such as transposon mutagenesis. Mutagenized bacteria are then transferred to Trypticase Soy Broth (TSB) liquid culture media containing an antibiotic. The bacteria are then cultured using standard methods, and the cultures are inspected for the presence of bacterial growth. Bacterial growth is compared between mutagenized cultures and wild-type control cultures. Bacterial growth can be identified, for example, by visual inspection, by

measuring optical density at 600 nm, or by other standard methods. The inability of a mutant to grow in liquid culture with antibiotics indicates the presence of a genetic mutation in a gene that regulates or is involved in phenotype-mediated or biofilm-mediated antibiotic resistance and biofilm formation. A gene identified using this method is subsequently isolated using standard procedures known in the art.

In another working example, a gene that regulates or is involved in phenotype-mediated or biofilm-mediated antibiotic resistance or biofilm formation is identified as follows. Bacteria are mutagenized using standard methods, such as transposon mutagenesis. Mutagenized bacteria are then plated on TSA plates containing antibiotic. These plates are cultured using standard methods, and then inspected for bacterial growth. The inability of a mutant to grow in TSA supplemented with antibiotics is taken as an indication of the presence of a genetic mutation in a gene that regulates or is involved in phenotype-mediated or biofilm-mediated resistance and biofilm formation. A gene identified using this method is subsequently isolated using standard procedures known in the art.

In another working example, a gene that regulates or is involved in phenotype-mediated or biofilm-mediated antibiotic resistance or biofilm formation is identified as follows. Bacteria are mutagenized using standard methods, such as transposon mutagenesis. Mutagenized bacteria are then transferred to liquid culture media TSB containing an antibiotic. The bacteria are then cultured using standard methods, and the cultures are inspected for the presence of bacterial growth. Bacterial growth is compared between mutagenized cultures and wild-type control cultures. Bacterial growth can be identified, for example, by visual inspection, by measuring optical density at 600 nm, or by other standard methods. The inability of a mutant to grow in liquid culture with antibiotics indicates the presence of a genetic mutation in a gene that regulates or is involved in phenotype-mediated or biofilm-mediated antibiotic resistance and biofilm formation. A gene identified using this method is subsequently isolated using standard procedures known in the art.

Each of the DNA sequences provided herein may also be used in the discovery and development of antipathogenic compounds (e.g., antibiotics). The encoded protein,

upon expression, can be used as a target for the screening of antibacterial drugs. Additionally, the DNA sequences encoding the amino terminal regions of the encoded protein or Shine-Delgarno or other translation facilitating sequences of the respective mRNA can be used to construct antisense sequences to control the expression of the coding sequence of interest.

The antagonists and agonists of the invention may be employed, for instance, to inhibit and treat a variety of bacterial infections, for example, those involving biofilm formation.

Optionally, compounds identified in any of the above-described assays may be confirmed as useful in conferring protection against the development of a pathogenic infection in any standard animal model (e.g., the mouse-burn assay described herein) and, if successful, may be used as anti-pathogen therapeutics (e.g, antibiotics).

Small molecules of the invention preferably have a molecular weight below 2,000 daltons, more preferably between 300 and 1,000 daltons, and most preferably between 400 and 700 daltons. It is preferred that these small molecules are organic molecules.

Test Compounds and Extracts

In general, compounds capable of reducing pathogenic virulence (e.g., reducing biofilm formation) are identified from large libraries of both natural product or synthetic (or semi-synthetic) extracts or chemical libraries according to methods known in the art. Those skilled in the field of drug discovery and development will understand that the precise source of test extracts or compounds is not critical to the screening procedure(s) of the invention. Accordingly, virtually any number of chemical extracts or compounds can be screened using the methods described herein. Examples of such extracts or compounds include, but are not limited to, plant-, fungal-, prokaryotic- or animal-based extracts, fermentation broths, and synthetic compounds, as well as modification of existing compounds. Numerous methods are also available for generating random or directed synthesis (e.g., semi-synthesis or total synthesis) of any number of chemical compounds, including, but not limited to, saccharide-, lipid-, peptide-, and nucleic acid-

based compounds. Synthetic compound libraries are commercially available from Brandon Associates (Merrimack, NH) and Aldrich Chemical (Milwaukee, WI). Alternatively, libraries of natural compounds in the form of bacterial, fungal, plant, and animal extracts are commercially available from a number of sources, including Biotics (Sussex, UK), Xenova (Slough, UK), Harbor Branch Oceangraphics Institute (Ft. Pierce, FL), and PharmaMar, U.S.A. (Cambridge, MA). In addition, natural and synthetically produced libraries are produced, if desired, according to methods known in the art, e.g., by standard extraction and fractionation methods. Furthermore, if desired, any library or compound is readily modified using standard chemical, physical, or biochemical methods.

In addition, those skilled in the art of drug discovery and development readily understand that methods for dereplication (e.g., taxonomic dereplication, biological dereplication, and chemical dereplication, or any combination thereof) or the elimination of replicates or repeats of materials already known for their anti-pathogenic activity should be employed whenever possible.

When a crude extract is found to have an anti-pathogenic or anti-virulence activity, or a binding activity, further fractionation of the positive lead extract is necessary to isolate chemical constituents responsible for the observed effect. Thus, the goal of the extraction, fractionation, and purification process is the careful characterization and identification of a chemical entity within the crude extract having anti-pathogenic activity. Methods of fractionation and purification of such heterogenous extracts are known in the art. If desired, compounds shown to be useful agents for the treatment of pathogenicity are chemically modified according to methods known in the art.

Pharmaceutical Therapeutics

The invention provides a simple means for identifying compounds (including peptides, small molecule inhibitors, and mimetics) capable of inhibiting the pathogenicity (e.g., biofilm formation) of a pathogen. Accordingly, a chemical entity discovered to have medicinal value using the methods described herein is useful as a

drug or as information for structural modification of existing anti-pathogenic compounds, e.g., by rational drug design. Such methods are useful for screening compounds having an effect on a variety of pathogens that form biofilms including, but not limited to, bacteria. Examples of pathogenic bacteria include, without limitation, *Aerobacter, Aeromonas, Acinetobacter, Agrobacterium, Bacillus, Bacteroides, Bartonella, Bortella, Brucella, Calymmatobacterium, Campylobacter, Citrobacter, Clostridium, Cornyebacterium, Enterobacter, Enterococcus, Escherichia, Francisella, Haemophilus, Hafnia, Helicobacter, Klebsiella, Legionella, Listeria, Morganella, Moraxella, Proteus, Providencia, Pseudomonas, Salmonella, Serratia, Shigella, Staphylococcus, Streptococcus, Treponema, Xanthomonas, Vibrio,* and *Yersinia.*

For therapeutic uses, the compositions or agents identified using the methods disclosed herein may be administered systemically, for example, formulated in a pharmaceutically-acceptable buffer such as physiological saline. Treatment may be accomplished directly, e.g., by treating the animal with antagonists which disrupt, suppress, attenuate, or neutralize the biological events associated with a pathogenicity polypeptide (e.g., a biofilm regulator polypeptide). Preferable routes of administration include, for example, subcutaneous, intravenous, interperitoneally, intramuscular, or intradermal injections which provide continuous, sustained levels of the drug in the patient. Treatment of human patients or other animals will be carried out using a therapeutically effective amount of an anti-pathogenic agent in a physiologically-acceptable carrier. Suitable carriers and their formulation are described, for example, in Remington's Pharmaceutical Sciences by E.W. Martin. The amount of the anti-pathogenic agent (e.g., an antibiotic) to be administered varies depending upon the manner of administration, the age and body weight of the patient, and with the type of disease and extensiveness of the disease. Generally, amounts will be in the range of those used for other agents used in the treatment of other microbial diseases, although in certain instances lower amounts will be needed because of the increased specificity of the compound. A compound is administered at a dosage that inhibits microbial proliferation (e.g., biofilm formation). If desired, such treatment is also performed in conjunction with standard antibiotic therapy.

Other Embodiments

In general, the invention includes any nucleic acid sequence which may be isolated as described herein or which is readily isolated by homology screening or PCR amplification using the nucleic acid sequences of the invention. Also included in the invention are polypeptides which are modified in ways which do not abolish their pathogenic activity (assayed, for example as described herein). Such changes may include certain mutations, deletions, insertions, or post-translational modifications, or may involve the inclusion of any of the polypeptides of the invention as one component of a larger fusion protein. Also, included in the invention are polypeptides that have lost their pathogenicity.

Thus, in other embodiments, the invention includes any protein which is substantially identical to a polypeptide of the invention. Such homologs include other substantially pure naturally-occurring polypeptides as well as allelic variants; natural mutants; induced mutants; proteins encoded by DNA that hybridizes to any one of the nucleic acid sequences of the invention under high stringency conditions or, less preferably, under low stringency conditions (e.g., washing at 2X SSC at 40°C with a probe length of at least 40 nucleotides); and proteins specifically bound by antisera of the invention.

The invention further includes analogs of any naturally-occurring polypeptide of the invention. Analogs can differ from the naturally-occurring the polypeptide of the invention by amino acid sequence differences, by post-translational modifications, or by both. Analogs of the invention will generally exhibit at least 85%, more preferably 90%, and most preferably 95% or even 99% identity with all or part of a naturally-occurring amino acid sequence of the invention. The length of sequence comparison is at least 15 amino acid residues, preferably at least 25 amino acid residues, and more preferably more than 35 amino acid residues. Again, in an exemplary approach to determining the degree of identity, a BLAST program may be used, with a probability score between e^{-3} and e^{-100} indicating a closely related sequence. Modifications include *in vivo* and *in vitro* chemical derivatization of polypeptides, e.g., acetylation, carboxylation, phosphorylation, or glycosylation; such modifications may occur during polypeptide

synthesis or processing or following treatment with isolated modifying enzymes. Analogs can also differ from the naturally-occurring polypeptides of the invention by alterations in primary sequence. These include genetic variants, both natural and induced (for example, resulting from random mutagenesis by irradiation or exposure to ethanemethylsulfate or by site-specific mutagenesis as described in Sambrook, Fritsch and Maniatis, *Molecular Cloning: A Laboratory Manual* (2d ed.), CSH Press, 1989, or Ausubel et al., *supra*). Also included are cyclized peptides, molecules, and analogs which contain residues other than L-amino acids, e.g., D-amino acids or non-naturally occurring or synthetic amino acids.

In addition to full-length polypeptides, the invention also includes fragments of any one of the polypeptides of the invention. As used herein, the term "fragment," means at least 5, preferably at least 20 contiguous amino acids, preferably at least 30 contiguous amino acids, more preferably at least 50 contiguous amino acids, and most preferably at least 60 to 80 or more contiguous amino acids. Fragments of the invention can be generated by methods known to those skilled in the art or may result from normal protein processing (e.g., removal of amino acids from the nascent polypeptide that are not required for biological activity or removal of amino acids by alternative mRNA splicing or alternative protein processing events).

Furthermore, the invention includes nucleotide sequences that facilitate specific detection of any of the nucleic acid sequences of the invention. Thus, for example, nucleic acid sequences described herein or fragments thereof may be used as probes to hybridize to nucleotide sequences by standard hybridization techniques under conventional conditions. Sequences that hybridize to a nucleic acid sequence coding sequence or its complement are considered useful in the invention. Sequences that hybridize to a coding sequence of a nucleic acid sequence of the invention or its complement and that encode a polypeptide of the invention are also considered useful in the invention. As used herein, the term "fragment," as applied to nucleic acid sequences, means at least 5 contiguous nucleotides, preferably at least 10 contiguous nucleotides, more preferably at least 20 to 30 contiguous nucleotides, and most preferably at least 40

to 80 or more contiguous nucleotides. Fragments of nucleic acid sequences can be generated by methods known to those skilled in the art.

The invention further provides a method for inducing an immunological response in an individual, particularly a human, which includes inoculating the individual with, for example, any of the polypeptides (or a fragment or analog thereof or fusion protein) of the invention to produce an antibody and/or a T cell immune response to protect the individual from infection, especially bacterial infection (e.g., a *Pseudomonas aeruginosa* infection). The invention further includes a method of inducing an immunological response in an individual which includes delivering to the individual a nucleic acid vector to direct the expression of a polypeptide described herein (or a fragment or fusion thereof) in order to induce an immunological response.

The invention also includes vaccine compositions including the polypeptides or nucleic acid sequences of the invention. For example, the polypeptides of the invention may be used as an antigen for vaccination of a host to produce specific antibodies which protect against invasion of bacteria. The invention therefore includes a vaccine formulation which includes an immunogenic recombinant polypeptide of the invention together with a suitable carrier.

The invention further provides compositions (e.g., nucleotide sequence probes), polypeptides, antibodies, and methods for the diagnosis of a pathogenic condition.

All publications and references, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference in their entirety as if each individual publication or reference were specifically and individually indicated to be incorporated by reference herein as being fully set forth. Any patent application to which this application claims priority is also incorporated by reference herein in its entirety in the manner described above for publications and references.

What is claimed is:

Claims

1. An isolated polypeptide comprising an amino acid sequence having at least 50% identity to the amino acid sequence of PvrR (SEQ ID NO:2), wherein expression of said polypeptide, in a microorganism, affects phenotype-mediated antibiotic-resistance in said microorganism.

2. The isolated polypeptide of claim 1, said polypeptide comprising the amino acid sequence of PvrR (SEQ ID NO:2).

3. The isolated polypeptide of claim 1, wherein said amino acid sequence consists essentially of the amino acid sequence of PvrR (SEQ ID NO:2) or a fragment thereof.

4. An isolated polypeptide fragment of the isolated polypeptide of claim 1.

5. The isolated polypeptide fragment of claim 4, wherein said polypeptide fragment comprises 200 contiguous amino acids of SEQ ID NO:2.

6. An isolated polynucleotide having at least 50% identity to the nucleotide sequence of *pvrR* (SEQ ID NO:1), wherein expression of said polynucleotide, in a microorganism, affects phenotype-mediated antibiotic-resistance in said microorganism.

7. The isolated polynucleotide of claim 6, said polynucleotide comprising the nucleotide sequence of *pvrR* (SEQ ID NO:1) or a complement thereof.

8. The isolated polynucleotide of claim 7, said polynucleotide consisting essentially of the nucleotide sequence of *pvrR* (SEQ ID NO:1) or a fragment thereof.

9. A vector comprising the isolated polynucleotide of any one of claims 6, 7, or 8.

10. A host cell comprising the vector of claim 9.

11. A screening method for identifying a compound that modulates gene expression of a regulator polynucleotide that affects phenotype-mediated antibiotic-resistance in a microorganism, said method comprising the steps of:

(a) providing a microbial cell comprising a polynucleotide having at least 50% identity to the nucleotide sequence of *pvrR* (SEQ ID NO:1), wherein expression of said polynucleotide, in said microbial cell, affects phenotype-mediated antibiotic-resistance in said microbial cell;

(b) contacting said microbial cell with a compound; and

(c) comparing the level of gene expression of said polynucleotide in the presence of said compound with the level of gene expression in the absence of said compound; wherein a measurable difference in gene expression indicates that said compound modulates gene expression of a regulator polynucleotide that affects phenotype-mediated antibiotic-resistance in a microorganism.

12. The method of claim 11, wherein said screening method identifyies a compound that increases transcription of said regulator polynucleotide.

13. The method of claim 11, wherein said screening method identifies a compound that decreases transcription of said regulator polynucleotide.

14. The method of claim 11, wherein said screening method identifies a compound that increases translation of an mRNA transcribed from said regulator polynucleotide.

15. The method of claim 11, wherein said screening method identifies a compound that decreases translation of an mRNA transcribed from said regulator polynucleotide.

16. The method of claim 11, wherein the compound is a member of a chemical library.

17. The method of claim 11, wherein said microbial cell belongs to the genus *Pseudomonas, Vibrio, Salmonella,* or *Staphylococcus.*

18. The method of claim 11, wherein said microbial cell is a phenotypic variant having increased biofilm formation.

19. The method of claim 18, wherein said phenotypic variant is a small colony variant.

20. The method of claim 19, wherein said small colony variant is a small colony variant of *Pseudomonas, Vibrio, Salmonella,* or *Staphylococcus.*

21. The method of claim 18, wherein said small colony variant is a rough small colony variant.

22. The method of claim 21, wherein said rough small colony variant is *Pseudomonas, Vibrio,* or *Salmonella.*

23. The method of claim 11, wherein the activity of the compound is dependent upon the presence of the *pvrR* gene (SEQ ID NO:1) or a functional equivalent thereof.

24. The method of claim 11, wherein said compound targets the *pvrR* gene (SEQ ID NO:1) or a functional equivalent thereof.

25. The method of claim 11, wherein expression of said polynucleotide mediates phenotypic switching of said microbial cell in the presence of a high concentration of an antibiotic.

26. The method of claim 11, wherein said polypeptide is expressed by the isolated polynucleotide of any one of claims 6, 7, or 8.

27. A screening method for identifying a compound that modulates an activity of a polypeptide that affects phenotype-mediated antibiotic-resistance in a microorganism, said method comprising the steps of:

(a) providing a microbial cell expressing a polypeptide having at least 50% identity to the amino acid sequence of PvrR (SEQ ID NO:2), wherein expression of said polypeptide, in said microbial cell, affects phenotype-mediated antibiotic-resistance in said microbial cell;

(b) contacting said microbial cell with a compound; and

(c) comparing an activity of said polypeptide in the presence of said compound with said activity in the absence of said compound; wherein a measurable difference in the activity indicates that said compound modulates said activity of said polypeptide that affects phenotype-mediated antibiotic-resistance in a microorganism.

28. The method of claim 27, wherein said screening method identifies a compound that increases the activity of said polypeptide.

29. The method of claim 27, wherein said screening method identifies a compound that decreases the activity of said polypeptide.

30. The method of claim 27, wherein the compound is a member of a chemical library.

31. The method of claim 27, wherein comparing the activity of the polypeptide involves an immunological assay.

32. The method of claim 27, wherein said microbial cell belongs to the genus *Pseudomonas*, *Vibrio*, *Salmonella*, or *Staphylococcus*.

33. The method of claim 27, wherein said microbial cell is a phenotypic variant having increased biofilm formation.

34. The method of claim 33, wherein said phenotypic variant is *Pseudomonas aeruginosa* PA14 RSCV.

35. The method of claim 27, wherein said regulator polypeptide is the isolated polypeptide of claim 1.

36. The method of claim 27, wherein the activity of the polypeptide regulates phenotypic switching.

37. The method of claim 27, wherein the activity of the polypeptide regulates biofilm-mediated antibiotic-resistance.

38. The method of claim 27, wherein the activity of the polypeptide affects susceptibility of the microbial cell to antibiotic treatment.

39. The method of claim 27, wherein said polypeptide is an element of a two-component regulatory system.

40. The method of claim 27, wherein the activity of the compound is dependent upon the presence of the PvrR polypeptide (SEQ ID NO:2) or a functional equivalent thereof.

41. The method of claim 27, wherein said compound targets the PvrR polypeptide (SEQ ID NO:2) or a functional equivalent thereof.

42. The method of claim 27, wherein said polypeptide mediates phenotypic switching of said microbial cell in the presence of a high concentration of an antibiotic.

43. The method of claim 27, wherein said polypeptide is expressed by the isolated polynucleotide of any one of claims 6, 7, or 8.

44. A screening method for identifying a compound that modulates microbial biofilm formation, said method comprising the steps of:

(a) culturing a microbial cell comprising a polypeptide having at least 50% identity to the amino acid sequence of PvrR (SEQ ID NO:2), wherein said microbial cell, upon culturing, forms a biofilm;

(b) contacting said microbial cell with a compound; and

(c) comparing microbial biofilm formation in the presence of said compound with microbial biofilm formation in the absence of said compound; wherein a measurable difference in said microbial biofilm formation indicates that said compound modulates biofilm formation.

45. The method of claim 44, wherein said screening method identifies a compound that increases biofilm formation.

46. The method of claim 44, wherein said screening method identifies a compound that decreases biofilm formation.

47. The method of claim 44, wherein biofilm formation is measured by assaying microbial aggregation.

48. The method of claim 47, wherein microbial aggregation is assayed using a microscope.

49. The method of claim 47, wherein microbial aggregation is assayed using a salt aggregation test.

50. The method of claim 47, wherein microbial aggregation is assayed using an attachment assay.

51. The method of claim 44, wherein the compound is a member of a chemical library.

52. The method of claim 44, wherein said microbial cell belongs to the genus *Pseudomonas*, *Vibrio*, *Salmonella*, or *Staphylococcus*.

53. The method of claim 44, wherein said microbial cell is a phenotypic variant having increased biofilm formation.

54. The method of claim 53, wherein said phenotypic variant is a small colony variant.

55. The method of claim 54, wherein said small colony variant is a small colony variant of *Pseudomonas*, *Vibrio*, *Salmonella*, or *Staphylococcus*.

56. The method of claim 54, wherein said small colony variant is a rough small colony variant.

57. The method of claim 56, wherein said rough small colony variant is *Pseudomonas*, *Vibrio*, or *Salmonella*.

58. The method of claim 44, wherein the activity of the compound is dependent upon the presence of PvrR polypeptide (SEQ ID NO: 2) or a functional equivalent thereof.

59. The method of claim 44, wherein said compound targets the PvrR polypeptide (SEQ ID NO:2) or a functional equivalent thereof.

60. The method of claim 44, wherein expression of said polypeptide mediates phenotypic switching of said microbial cell in the presence of a high concentration of an antibiotic.

61. The method of claim 44, wherein said polypeptide is an isolated polypeptide of any one of claims 1, 2, or 3.

62. A method of treating a microbial infection involving a microorganism that forms a biofilm in a mammal, said method comprising administering to said mammal a therapeutically-effective amount of a compound that induces the expression of or activity of or represses the expression of or activity of the polypeptide of any one of claims 1, 2, or 3.

63. The method of claim 62, wherein said method further comprises administering to said mammal a therapeutically-effective amount of an antibiotic.

64. The method of claim 62, wherein said mammal is a human.

65. The method of claim 62, wherein said human has cystic fibrosis.

66. The method of claim 62, wherein said human has a chronic infection.

67. The method of claim 62, wherein the said microorganism belongs to the genus *Pseudomonas*, *Vibrio*, *Salmonella* or *Staphylococcus*.

68. A method of cleaning or disinfecting a surface at least partially covered by a microorganism that forms a biofilm, said method comprising contacting said microorganism with a cleaning composition comprising a compound that induces the expression of or activity of or represses the expression of or activity of the polypeptide of claim 1, 2, or 3.

69. The method of claim 68, wherein said microorganism belongs to the genera *Pseudomonas*, *Vibrio*, *Salmonella* or *Staphylococcus*.

70. A screening method for identifying a compound that decreases pathogenicity of an antibiotic-resistant phenotypic variant, said method comprising the steps of:

(a) contacting an antibiotic-resistant phenotypic variant with a candidate compound; and

(b) measuring reversion of said antibiotic-resistant phenotypic variant to a wild-type phenotype, an increase in reversion indicating that said compound decreases pathogenicity of said antibiotic-resistant phenotypic variant.

71. The method of claim 70, wherein said antibiotic-resistant phenotypic variant is a bacterial variant.

72. The method of claim 71, wherein said antibiotic-resistant phenotypic bacterial variant is cultured in the absence of an antibiotic.

73. The method of claim 71, wherein said antibiotic-resistant phenotypic bacterial variant has increased biofilm formation.

74. The method of claim 71, wherein said antibiotic-resistant phenotypic bacterial variant is a rough small colony variant.

75. The method of claim 71, wherein said antibiotic-resistant phenotypic bacterial variant is a hyperpiliated variant.

76. The method of claim 71, wherein said antibiotic-resistant phenotypic bacterial variant has increased hydrophobicity.

77. The method of claim 71, wherein said antibiotic-resistant phenotypic bacterial variant has an alteration in a surface component.

78. The method of claim 71, wherein said antibiotic-resistant phenotypic bacterial variant is a pathogen.

79. The method of claim 78, wherein said pathogen is a Gram positive bacterium.

80. The method of claim 79, wherein said pathogen is *Staphylococcus.*

81. The method of claim 78, wherein said pathogen is a Gram negative bacterium.

82. The method of claim 75, wherein said pathogen is *Vibrio*, *Pseudomonas*, or *Salmonella.*

83. A screening method for identifying a compound that decreases pathogenicity of a wild-type microbe, said method comprising the steps of:

(a) culturing a wild-type microbe with a candidate compound in the presence of an antibiotic; and

(b) comparing the number of antibiotic-resistant phenotypic variants in the presence of said compound to the number of antibiotic-resistant phenotypic variants in the absence of said compound, a decrease in the number of said antibiotic-resistant phenotypic variants in the presence of said compound indicating that said compound decreases pathogenicity of said wild-type microbe.

84. A screening method for identifying a polynucleotide encoding a regulator polypeptide that modulates an antibiotic-resistant phenotype of a microorganism, said method comprising the steps of:

(a) identifying an antibiotic-resistant phenotypic variant of a microorganism comprising a first phenotype;

(b) mutagenizing said antibiotic-resistant phenotypic variant of said microorganism, thereby generating a mutated phenotypic variant of said microorganism; and

(c) selecting said mutated phenotypic variant of step (b) having a second phenotype, other than the first phenotype of said antibiotic-resistant phenotypic variant, wherein said second phenotype identifies a mutation in said mutated phenotypic variant of step (b); and

(d) using said mutation for identifying a polynucleotide encoding a regulator polypeptide that modulates an antibiotic-resistant phenotype of a microorganism.

85. The method of claim 84, wherein said second phenotype comprises a wild-type phenotype.

86. A screening method for identifying a polynucleotide encoding a regulator polypeptide that modulates phenotype-mediated antibiotic-resistance of a microorganism, said method comprising the steps of:

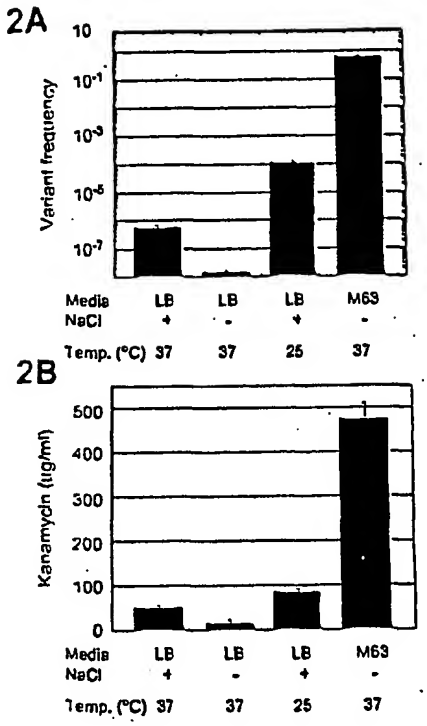
(a) transforming an antibiotic-resistant phenotypic variant of a microorganism with a candidate polynucleotide encoding a regulator polypeptide; and

(b) culturing said transformed antibiotic-resistant phenotypic variant of a microorganism under conditions suitable for expression of said regulator polypeptide; and

(c) measuring reversion of said transformed antibiotic-resistant phenotypic variant of said microorganism to a wild-type phenotype, an increase in reversion identifies said polynucleotide as encoding a regulator polypeptide that modulates phenotype-mediated antibiotic-resistance.

87. The method of claim 80, wherein said polynucleotide encodes a regulator polypeptide that modulates a phenotypic switch from antibiotic-resistant phenotype to an antibiotic-susceptible phenotype.

88. The method of claim 80, wherein said polynucleotide having at least 50% identity to the nucleotide sequence of *pvrR* (SEQ ID NO:1) encodes an element of a two-component regulatory system.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10^{-1}
10^{-3}
10^{-5}
10^{-7}
Variant frequency
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NaCl + - + -
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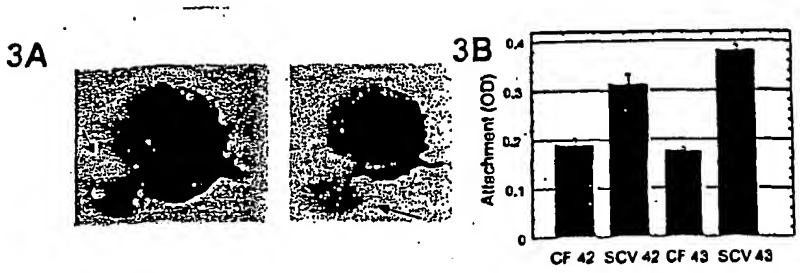
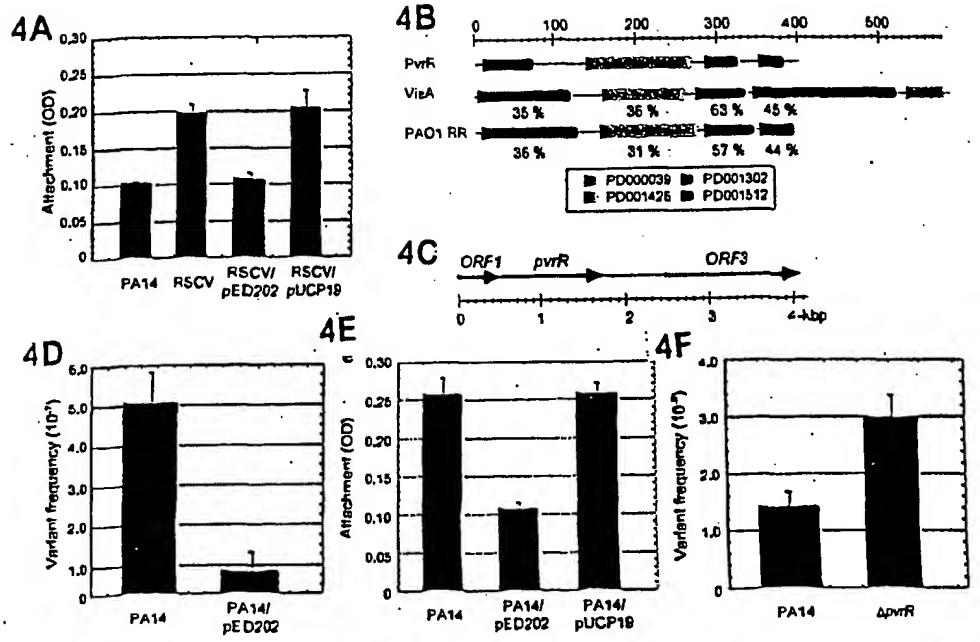
2B
500
400
300
200
100
0
Kanamycin (ug/ml)
Media LB LB LB M63
NaCl + - + -
Temp. (°C) 37 37 25 37

Figures 2 A-B



Figures 3A-B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RSCV/ pED202
RSCV/ pUCP19
4B
PvrR
VisA
PAO1 RR
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36 %
63 %
45 %
36 %
31 %
57 %
44 %
PD000039
PD001302
PD001426
PD001512
4C
ORF1
pvrR
ORF3
4D
Variant frequency
PA14
PA14/ pED202
4E
Attachment (OD)
PA14
PA14/ pED202
PA14/ pUCP19
4F
Variant frequency
PA14
ΔpvrR

Figures 4 A-F

Figure 5A, *pvrR* (SEQ ID NO:1)

```
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Figure 5B

ORF1-12
SEQ ID NO:3

```
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gacctagagt gcgtggaatt ctccccgctg gaattgaccg aagaggtcgt gcagtcgttc 240
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Figure 5C *ORF3* (SEQ ID NO:5)

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```

Figure 5D PvrR (SEQ ID NO:2)

```
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Gln Arg Glu Tyr Leu Leu Asn Leu Phe Arg Glu Arg Gly Val Gln Tyr
            20                  25                  30
Leu Val Gly Ala Gly Asp Gly Ala Glu Ala Leu Arg Cys Leu Lys Gln
        35                  40                  45
Asp Arg Phe Asp Leu Ile Leu Ser Asp Leu Met Met Pro Gly Met Asp
    50                  55                  60
Gly Ile Gln Met Ile Leu Gln Leu Pro Tyr Leu Lys His Arg Pro Lys
65                  70                  75                  80
Leu Ala Leu Met Ser Ser Ser Ser Gln Arg Met Met Leu Ser Ala Ser
                85                  90                  95
Arg Val Ala Gln Ser Leu Gly Leu Ser Val Ile Asp Leu Leu Pro Lys
            100                 105                 110
Pro Thr Leu Pro Lys Ala Ile Gly Gln Leu Leu Glu His Leu Glu Arg
        115                 120                 125
Cys Leu Arg Gln Lys Leu Glu Pro Glu Thr Asp Glu Thr Pro His Gly
    130                 135                 140
Arg Thr Ala Leu Leu Asp Ala Leu His Asn Glu Gln Leu Val Thr Trp
145                 150                 155                 160
Phe Gln Ala Lys Lys Ser Leu His Thr Gly Arg Ile Val Gly Ala Glu
                165                 170                 175
Ala Leu Ile Arg Trp Ser His Pro Gln His Gly Leu Leu Leu Pro Ser
            180                 185                 190
Cys Phe Met Ser Asp Val Asp Ala Thr Gly Leu His Glu Ala Leu Leu
        195                 200                 205
Trp Arg Val Leu Glu Gln Thr Leu Asn Ala Gln Glu Ser Trp Arg Arg
    210                 215                 220
Ala Gly Tyr Glu Ile Pro Val Ser Val Asn Leu Pro Pro His Leu Leu
225                 230                 235                 240
Asp Asn Gln Glu Leu Pro Asp Arg Leu Tyr Glu Tyr Val Gly Ala Arg
                245                 250                 255
Gly Ala Cys Thr Ser Ser Leu Cys Phe Glu Leu Thr Glu Ser Ser Val
            260                 265                 270
Thr Thr Leu Ser Ser Asn Tyr Tyr Ala Gly Ala Cys Arg Leu Arg Met
        275                 280                 285
Lys Gly Phe Gly Leu Ala Gln Asp Asp Phe Gly Gln Gly Tyr Ser Ser
    290                 295                 300
Phe Tyr Asn Leu Val Thr Thr Pro Phe Thr Glu Leu Lys Ile Asp Arg
305                 310                 315                 320
Ser Leu Val Gln Gly Cys Val Glu Asp Asn Gly Leu Asn Ala Ala Val
                325                 330                 335
Ile Ser Cys Ile Glu Leu Gly His Arg Leu Asn Leu Asp Val Val Ala
            340                 345                 350
Glu Gly Val Glu Thr Cys Glu Glu Leu Asn Leu Leu Arg Arg Leu Gly
        355                 360                 365
Cys Asp Arg Ala Gln Gly Phe Leu Ile Ser Lys Ala Val Ser Ala Arg
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Glu Phe Glu Arg Gln Leu Arg Glu Asp Gly Pro Ser Leu Leu Val
385                 390                 395
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Figure 5E

ORF1-12
SEQ ID NO:4

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Lys Ala Ile Gln His Ser Ser Ser Thr Leu Leu Gln Leu Ile Ser Asp
        35                  40                  45
Val Leu Asp Val Ser Lys Ile Glu Ala Gly Gln Leu Asp Leu Glu Cys
    50                  55                  60
Val Glu Phe Ser Pro Leu Glu Leu Thr Glu Glu Val Val Gln Ser Phe
65                  70                  75                  80
Thr Gly Ala Ala Gln Ala Lys Gly Leu Gln Leu Tyr Thr Cys Leu Ser
                85                  90                  95
Ala Glu Leu Pro Leu Arg Met Arg Gly Ala Ala Ala Ser Ile Arg Gln
            100                 105                 110
Ile Leu Asn Asn Leu Leu Ser Asn Ala Val Lys Phe Thr Asp Asn Gly
        115                 120                 125
Tyr Val Asn Val His Leu Lys Ala Ser Val Val Asp Ala Glu Cys Val
    130                 135                 140
Met Leu Thr Trp Gln Val Asn Asp Thr Gly Met Gly Ile Asn Val Glu
145                 150                 155                 160
Asp Gln Pro Arg Leu Phe Glu Pro Phe Tyr Gln Ile Arg Arg Ser Glu
                165                 170                 175
His Pro Val Ala Gly Thr Gly Leu Gly Leu Ser Ile Ser Gln Arg Leu
            180                 185                 190
Ala Gln Leu Met Asn Gly Ser Leu Lys Leu Val Ser Glu Leu Gly Leu
        195                 200                 205
Gly Ser Ser Phe Ser Leu Arg Leu Pro Leu Glu Arg Ile Ala Met Gln
    210                 215                 220
Ala Glu Pro Gln Asp Leu Ala Gly Cys Ala Val Gln Val Leu Ala Pro
225                 230                 235                 240
Val Arg Asp Leu Thr Glu Cys Leu Cys Gly Trp Ile Ser Arg Trp Gly
                245                 250                 255
Gly Arg Ala Met Val Ala Thr Pro Arg Ser Leu Asp Glu Ala Asp Ala
            260                 265                 270
Thr Ser Leu Leu Val Glu Val Leu Leu Leu Glu Gly Ala Pro Met Phe
        275                 280                 285
Glu Ala Trp Pro Gly Cys Arg Val Glu Leu Ser Pro Gln Gly Asp Met
    290                 295                 300
Glu Pro Gln Ala Gln Gly Arg Asp Trp Leu Leu Gly Leu Asn Asn Leu
305                 310                 315                 320
Asp Gly Leu His Arg Ala Leu Gly Leu Ala His Gly Arg Leu Ala Asp
                325                 330                 335
Pro Ser Thr Pro Pro Ile Arg Leu Ala Pro Leu Arg Asn Leu Gly Leu
            340                 345                 350
Arg Val Leu Val Val Glu Asp Asn Ala Ile Asn Gln Leu Ile Leu Arg
        355                 360                 365
Asp Gln Met Glu Ala Leu Gly Cys Ser Val Glu Leu Leu Phe Asp Gly
    370                 375                 380
Arg Glu Ala Leu Leu His Cys Gln Thr Ala Cys Phe Asp Val Val Leu
385                 390                 395                 400
Thr Asp Ile Asn Met Pro Asn Met Asn Gly Tyr Glu Leu Thr Ala Glu
                405                 410                 415
Leu Arg Arg Gln Gly Phe Arg Gln Pro Ile Ile Gly Ala Thr Ala Asn
            420                 425                 430
Ala Met Arg Glu Glu Arg Glu Arg Cys Met Ser Ala Gly Met Asn Asp
        435                 440                 445
Cys Leu Val Lys Pro Val Asp Leu Asn Ala Leu Gln Asn Cys Leu Ile
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450 455 460
Asn Ile Leu Lys Val Asp Arg
465 470

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Figure 5F, ORF3 (SEQ ID NO:6)

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Met Met Asp Val Ile Arg Glu His Glu Val Phe Leu Gly Arg Ile Ala
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Arg Lys Ser Asp Lys Thr Thr Gln Lys Tyr Asp Tyr Asp Val Val Pro
            20                  25                  30
Leu Gln Arg His Leu Leu Ala Lys Glu Asn Gly Leu Ala Val Tyr Glu
        35                  40                  45
Gly Arg Glu Phe Ser Phe Ala Met Pro Phe Leu Leu Ala Thr Lys His
    50                  55                  60
Ala Leu Ser Ala Asp Ser Ser Gly Asp Pro Phe Ser Leu Gly Val Leu
65                  70                  75                  80
Leu Ala Asn Phe Tyr Gly Ser Phe Trp Ser Val Ser Ala Tyr Pro Ala
                85                  90                  95
Pro Gln Leu Leu Ile Phe Asp Leu Ser Gly Ser Thr Arg Leu Ala Val
            100                 105                 110
Pro Ser Ile Pro Ser Thr Ala Gln Arg Asp Arg Leu Ser Gly Ser Tyr
        115                 120                 125
Pro Met Ile Val Glu Arg Ile Leu Ala Arg Leu Arg Thr Arg Pro Val
    130                 135                 140
Gly Glu Asp Ala Gln Arg Val His Trp Ile Arg Ala Asp Arg Tyr Arg
145                 150                 155                 160
Asp Ser Ala Leu Glu Met Leu Gly Val Ala Arg Val Asp Leu Pro Glu
                165                 170                 175
Thr Leu Trp Trp His Asp Glu Pro Asn His Leu Ile Ile Ala Ala Ser
            180                 185                 190
Leu Leu Asp Leu Arg Arg Ile Asn Asp Phe Glu Gln Leu Val Glu Arg
        195                 200                 205
Pro Ala Phe Asp Ser Tyr Ser Leu Val Ser Pro Asp Gly Glu Val Leu
    210                 215                 220
Leu Gly Ala Ala Pro Ala Thr Gly Leu Arg Asp Gly Leu Asn Leu Thr
225                 230                 235                 240
Arg Gln Gly Val Ala Val Gln Leu Arg Ser Gln Pro Glu Asn Gly Trp
                245                 250                 255
Leu Ala Val Tyr Arg Thr Asp Tyr Gly Asn Phe Phe Arg His Ser Arg
            260                 265                 270
Trp Leu Val Ala Gly Leu Leu Leu Thr Pro Ala Leu Leu Leu Ala Gly
        275                 280                 285
Trp Leu Gly Met Arg Trp Tyr Thr Ser Ser Val Val Asn Pro Val His
    290                 295                 300
Arg Ala His Arg Gln Leu Val Glu Ser Asp Thr Phe Ser Arg Thr Leu
305                 310                 315                 320
Ile Gln Thr Ala Pro Val Ala Leu Val Val Leu Thr Gln Asp Asp Gln
                325                 330                 335
Gln Leu Val Thr Cys Asn His Leu Ala Ala Gln Trp Leu Gly Gly Pro
            340                 345                 350
Thr Glu Ile Leu Gly Leu Thr Ser Asn Trp Lys Leu Phe Asp Ala Arg
        355                 360                 365
Gly Gln Val Pro Gly Asp Ile Cys Ile Gln Val Gly Gly Arg Tyr Leu
    370                 375                 380
Gln Thr Ala Phe Ala Ala Thr Arg Tyr Ala Gly Thr Glu Ala Val Leu
385                 390                 395                 400
Cys Val Phe Asn Asp Ile Thr Val His Cys Glu Ala Glu Thr Ala Leu
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Ser Asn Ala Lys Arg Ala Ala Asp Ala Ala Ser Gln Ala Lys Thr Leu
            420                 425                 430
Phe Leu Ala Arg Met Ser His Glu Ile Arg Thr Pro Leu Tyr Gly Val
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Figure 5F Continued

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465                 470                 475                 480
Leu Ile Ser Asp Val Leu Asp Val Ser Lys Ile Glu Ala Gly Gln Met
                485                 490                 495
Ala Leu Thr Leu Ala Ala Phe Asn Pro Leu Asp Leu Val Arg Glu Val
            500                 505                 510
Leu Gly Asn Phe Ala Ala Ser Ala Met Ala Lys Asp Leu Gln Val Asp
        515                 520                 525
Pro Leu Asp Thr Leu Ala Leu Glu Ala Gln Val Ala His Gly Phe Glu
    530                 535                 540
Glu Ser Val Leu Phe Glu Val Ala Gly Gly Ser Val Gly His Phe Glu
545                 550                 555                 560
Glu Gly Val Val Gly Val Val Glu Gln Arg Leu Gln Arg Leu Phe Gln
                565                 570                 575
Leu Gln Arg Arg Leu Val Ala His Leu His Glu Asp Asp Arg Gln Ala
            580                 585                 590
Pro Arg Ser Gly Val Arg Arg Arg Leu Gly Ser Asp Pro Gly Gln Val
        595                 600                 605
His His Ile Gly Ile Val Leu His Arg Asp Ser Pro Ala Thr Leu Ala
    610                 615                 620
Ala Ala His Gly Met Ala Lys Ile Gly His Arg Gly Ser Ile Gly Val
625                 630                 635                 640
Val Arg Asn Val Asn Phe Gln Ala Ser Lys Thr Ser Ile Tyr Ile His
                645                 650                 655
Tyr Arg Asp Thr Phe Lys Ser Arg
            660
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Figure 5G

SEQ ID NO:7

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ggcatggaagt tgaagaattt cttacagcct tttgatagcg gtttctccac tccgagtgct 180
gcgctcaagc tgctccgcat gctcggtggc gccttgatgt tgtgcgtgct atgcagcctg 240
atattcagtg tgagcatggt tttaaaccat caggtgtccc tcagtcggca agctatgaat 300
gtggctatgt acgaagcgca gctttatttc gagcagcgcg aggcgttgct caatcacttg 360
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Figure 6A

ORF1-1
SEQ ID NO: 8

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Figure 6B

ORF1-2
SEQ ID No:9

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Figure 6C

ORF1-3
SEQ ID NO:10

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Figure 6D

ORF1-4
SEQ ID NO:11

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Figure 6E

ORF1-5
SEQ ID NO:12

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Figure 6F

ORF1-6
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Figure 6G

ORF1-7
SEQ ID NO:14

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ctgtgcgtgc tgcgtcgtgc cgacgccgca gtggtcctgg aaaatcccca ggcgcgccaa 720
tggctgggtg atagcgaggc gattgcccac gacgcgccga gatggatttc ccaggcgttc 780
gcaggaggtg tgaagtgttc tggagaagaa ctggaaaccg aggcagggct acatcttcat 840
ctcaattaca cgcccacccg ctataacggt gaagacgtat tgttctgcgc cttcagtgaa 900
atcagtgcac gcaagcggat ggaggcggaa ctggctcgcg caaaatccct ggcggatgct 960
gccaatgaag ccaagacgct gtttctcgcc accatgagcc atgaaatccg cacacctctg 1020
tacggcatgc ttggcacgct tgagctgctt gggcgtaccg agctgagtcg gcagcaggcc 1080
ggttacctaa aggcaatcca gcattcctcg tcgaccctgc tgcaactgat cagcgatgtg 1140
cttgacgtat ccaagataga ggccggccaa ctggacctag agtgcgtgga attctccccg 1200
ctggaattga ccgaagaggt cgtgcagtcg ttcaccggtg ccgcgcaggc caaggggctg 1260
cagttgtata cctgcctctc tgcggagctg ccgctgcgca tgcgggggcc cgcggcgtcg 1320
atccggcaga ttctcaacaa cctgctgagc aacgcggtga agttcaccga caatggctat 1380
gtcaacgtcc acctgaaggc cagcgtggtc gatgccgaat gtgtgatgct gacctggcag 1440
gtcaacgata ccggcatggg gatcaacgtc gaggatcagc cgcgtctgtt cgaaccgttc 1500
taccagatac gccgctccga gcatccggtc gcaggcacgg gcctcggctt gtcgatcagc 1560
cagcgcctgg cgcagctaat gaatggcagt ctgaaactgg tcagtgagct ggggttgggc 1620
agcagcttta gcctcaggct tccgcttgag cggatcgcga tgcaggctga gccgcaggac 1680
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gcggacgcga cctcgctgct ggtcgaagtg ttactgctgg aggggcgcc gatgttcgaa 1860
gcatggccag gatgccgggt ggagctttcc cctcagggtg atatggagcc gcaggcacag 1920
ggccgcgact ggctgctcgg gctcaacaac ctggacggcc tgcatcgtgc tctgggcctg 1980
gcccatgggc gtctcgctga tccttcgacg ccgccgatac ggctggctcc gttgcgcaat 2040
ctaggtctcc gcgtcctagt ggtggaggat aacgcgatca accagttgat cttgagggac 2100
cagatggaag cgctgggctg cagcgtggag ctgctcttcg atggtcgcga ggcgttgctg 2160
cactgccaga cggcctgctt cgacgtggtg ctcaccgata tcaacatgcc gaacatgaac 2220
ggatacgagc taaccgcgga gctacggcgc caagggttcc ggcagccgat catcggcgcg 2280
acggcgaacg ccatgcgtga ggagcgcgag cgctgcatgt ccgccgggat gaacgattgc 2340
ctggtcaaac cggtggatct gaatgccctt cagaactgct tgattaatat tctcaaggtg 2400
gatcgatga                                                        2409
```

Figure 6H

ORF1-8
SEQ ID NO:15

```
atgttgcgcc ggaatgatgc cggaaactac atgctgctgg atcagcatgg gcaggtcgta 60
ctcgctacgg acgcagaggc gctggggagc ggtgcgtcgc ggacgctttt gcgtggagac 120
ggcttcggtt tcatcggtgc tggcccactg ccgcagcata tggtgctttt ccagcacgtg 180
gggtcttcga gctgggatct gatctatcac atcggtatcg gtcgcctgtt gctggctctg 240
tggctccctc tgttacttgc ctctgcgttg gcactcgcag tcggcatcct actgcattgg 300
ctggtgcgga gcatcgagcg acgcttgata gagcccgcaa agcgacgcct tgaagcattg 360
aaggagagcg aagccttttc ccgtgcagtt atccaggccg cgcccgtcgc gctgtgcgtg 420
ctgcgtcgtg ccgacgccgc agtggtcctg gaaaatcccc aggcgcgcca atggctgggt 480
gatagcgagg cgattgccca cgacgcgccg agatggattt cccaggcgtt cgcaggaggt 540
gtgaagtgtt ctggagaaga actggaaacc gaggcagggc tacatcttca tctcaattac 600
acgcccaccc gctataacgg tgaagacgta ttgttctgcg ccttcagtga aatcagtgca 660
cgcaagcgga tggaggcgga actggctcgc gcaaaatccc tggcggatgc tgccaatgaa 720
gccaagacgc tgtttctcgc caccatgagc catgaaatcc gcacacctct gtacggcatg 780
cttggcacgc ttgagctgct tgggcgtacc gagctgagtc ggcagcaggc cggttaccta 840
aaggcaatcc agcattcctc gtcgaccctg ctgcaactga tcagcgatgt gcttgacgta 900
tccaagatag aggccggcca actggaccta gagtgcgtgg aattctcccc gctggaattg 960
accgaagagg tcgtgcagtc gttcaccggt gccgcgcagg ccaaggggct gcagttgtat 1020
acctgcctct ctgcggagct gccgctgcgc atgcgggggg ccgcggcgtc gatccggcag 1080
attctcaaca acctgctgag caacgcggtg aagttcaccg acaatggcta tgtcaacgtc 1140
cacctgaagg ccagcgtggt cgatgccgaa tgtgtgatgc tgacctggca ggtcaacgat 1200
accggcatgg ggatcaacgt cgaggatcag ccgcgtctgt tcgaaccgtt ctaccagata 1260
cgccgctccg agcatccggt cgcaggcacg ggcctcggct tgtcgatcag ccagcgcctg 1320
gcgcagctaa tgaatggcag tctgaaactg gtcagtgagc tggggttggg cagcagcttt 1380
agcctcaggc ttccgcttga gcggatcgcg atgcaggctg agccgcagga cctagccggg 1440
tgcgccgtcc aagtgctggc gcctgtccgc gacctaacgg aatgcctgtg tggctggatc 1500
tcccgctggg gtggaagggc catggtcgcg acgccgaggt cgctggacga ggcggacgcg 1560
acctcgctgc tggtcgaagt gttactgctg gaggggcgc cgatgttcga agcatggcca 1620
ggatgccggg tggagctttc ccctcagggt gatatggagc cgcaggcaca gggccgcgac 1680
tggctgctcg ggctcaacaa cctggacggc ctgcatcgtg ctctgggcct ggcccatggg 1740
cgtctcgctg atccttcgac gccgccgata cggctggctc cgttgcgcaa tctaggtctc 1800
cgcgtcctag tggtggagga taacgcgatc aaccagttga tcttgaggga ccagatggaa 1860
gcgctgggct gcagcgtgga gctgctcttc gatggtcgcg aggcgttgct gcactgccag 1920
acggcctgct tcgacgtggt gctcaccgat atcaacatgc cgaacatgaa cggatacgag 1980
ctaaccgcgg agctacggcg ccaagggttc cggcagccga tcatcggcgc gacggcgaac 2040
gccatgcgtg aggagcgcga gcgctgcatg tccgccggga tgaacgattg cctggtcaaa 2100
ccggtggatc tgaatgccct tcagaactgc ttgattaata ttctcaaggt ggatcgatga 2160
```

Figure 6I

ORF1-9
SEQ ID NO:16

```
atgctgctgg atcagcatgg gcaggtcgta ctcgctacgg acgcagaggc gctggggagc 60
ggtgcgtcgc ggacgctttt gcgtggagac ggcttcggtt tcatcggtgc tggcccactg 120
ccgcagcata tggtgctttt ccagcacgtg gggtcttcga gctgggatct gatctatcac 180
atcggtatcg gtcgcctgtt gctggctctg tggctccctc tgttacttgc ctctgcgttg 240
gcactcgcag tcggcatcct actgcattgg ctggtgcgga gcatcgagcg acgcttgata 300
gagcccgcaa agcgacgcct tgaagcattg aaggagagcg aagccttttc ccgtgcagtt 360
atccaggccg cgcccgtcgc gctgtgcgtg ctgcgtcgtg ccgacgccgc agtggtcctg 420
gaaaatcccc aggcgcgcca atggctgggt gatagcgagg cgattgccca cgacgcgccg 480
agatggattt cccaggcgtt cgcaggaggt gtgaagtgtt ctggagaaga actggaaacc 540
gaggcagggc tacatcttca tctcaattac acgcccaccc gctataacgg tgaagacgta 600
ttgttctgcg ccttcagtga aatcagtgca cgcaagcgga tggaggcgga actggctcgc 660
gcaaaatccc tggcggatgc tgccaatgaa gccaagacgc tgtttctcgc caccatgagc 720
catgaaatcc gcacacctct gtacggcatg cttggcacgc ttgagctgct tgggcgtacc 780
gagctgagtc ggcagcaggc cggttaccta aaggcaatcc agcattcctc gtcgaccctg 840
ctgcaactga tcagcgatgt gcttgacgta tccaagatag aggccggcca actggaccta 900
gagtgcgtgg aattctcccc gctggaattg accgaagagg tcgtgcagtc gttcaccggt 960
gccgcgcagg ccaaggggct gcagttgtat acctgcctct ctgcggagct gccgctgcgc 1020
atgcgggggg ccgcggcgtc gatccggcag attctcaaca acctgctgag caacgcggtg 1080
aagttcaccg acaatggcta tgtcaacgtc cacctgaagg ccagcgtggt cgatgccgaa 1140
tgtgtgatgc tgacctggca ggtcaacgat accggcatgg ggatcaacgt cgaggatcag 1200
ccgcgtctgt tcgaaccgtt ctaccagata cgccgctccg agcatccggt cgcaggcacg 1260
ggcctcggct tgtcgatcag ccagcgcctg gcgcagctaa tgaatggcag tctgaaactg 1320
gtcagtgagc tggggttggg cagcagcttt agcctcaggc ttccgcttga gcggatcgcg 1380
atgcaggctg agccgcagga cctagccggg tgcgccgtcc aagtgctggc gcctgtccgc 1440
gacctaacgg aatgcctgtg tggctggatc tcccgctggg gtggaagggc catggtcgcg 1500
acgccgaggt cgctggacga ggcggacgcg acctcgctgc tggtcgaagt gttactgctg 1560
gaggggcgc cgatgttcga agcatggcca ggatgccggg tggagcttc ccctcagggt 1620
gatatggagc cgcaggcaca gggccgcgac tggctgctcg ggctcaacaa cctggacggc 1680
ctgcatcgtg ctctgggcct ggcccatggg cgtctcgctg atccttcgac gccgccgata 1740
cggctggctc cgttgcgcaa tctaggtctc cgcgtcctag tggtggagga taacgcgatc 1800
aaccagttga tcttgaggga ccagatggaa gcgctgggct gcagcgtgga gctgctcttc 1860
gatggtcgcg aggcgttgct gcactgccag acggcctgct tcgacgtggt gctcaccgat 1920
atcaacatgc cgaacatgaa cggatacgag ctaaccgcgg agctacggcg ccaagggttc 1980
cggcagccga tcatcggcgc gacggcgaac gccatgcgtg aggagcgcga gcgctgcatg 2040
tccgccggga tgaacgattg cctggtcaaa ccggtggatc tgaatgccct tcagaactgc 2100
ttgattaata ttctcaaggt ggatcgatga                                  2130
```

Figure 6J

ORF1-10
SEQ ID NO:17

atggtgcttt tccagcacgt ggggtcttcg agctgggatc tgatctatca catcggtatc 60
ggtcgcctgt tgctggctct gtggctccct ctgttacttg cctctgcgtt ggcactcgca 120
gtcggcatcc tactgcattg gctggtgcgg agcatcgagc gacgcttgat agagcccgca 180
aagcgacgcc ttgaagcatt gaaggagagc gaagcctttt cccgtgcagt tatccaggcc 240
gcgcccgtcg cgctgtgcgt gctgcgtcgt gccgacgccg cagtggtcct ggaaaatccc 300
caggcgcgcc aatggctggg tgatagcgag gcgattgccc acgacgcgcc gagatggatt 360
tcccaggcgt tcgcaggagg tgtgaagtgt tctggagaag aactggaaac cgaggcaggg 420
ctacatcttc atctcaatta cacgcccacc cgctataacg gtgaagacgt attgttctgc 480
gccttcagtg aaatcagtgc acgcaagcgg atggaggcgg aactggctcg cgcaaaatcc 540
ctggcggatg ctgccaatga agccaagacg ctgtttctcg ccaccatgag ccatgaaatc 600
cgcacacctc tgtacggcat gcttggcacg cttgagctgc ttgggcgtac cgagctgagt 660
cggcagcagg ccggttacct aaaggcaatc cagcattcct cgtcgaccct gctgcaactg 720
atcagcgatg tgcttgacgt atccaagata gaggccggcc aactggacct agagtgcgtg 780
gaattctccc cgctggaatt gaccgaagag gtcgtgcagt cgttcaccgg tgccgcgcag 840
gccaaggggc tgcagttgta tacctgcctc tctgcggagc tgccgctgcg catgcggggg 900
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ttcgaaccgt tctaccagat acgccgctcc gagcatccgg tcgcaggcac gggcctcggc 1140
ttgtcgatca gccagcgcct ggcgcagcta atgaatggca gtctgaaact ggtcagtgag 1200
ctggggttgg gcagcagctt tagcctcagg cttccgcttg agcggatcgc gatgcaggct 1260
gagccgcagg acctagccgg gtgcgccgtc caagtgctgg cgcctgtccg cgacctaacg 1320
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ccgcaggcac agggccgcga ctggctgctc gggctcaaca acctggacgg cctgcatcgt 1560
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ccgttgcgca atctaggtct ccgcgtccta gtggtggagg ataacgcgat caaccagttg 1680
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ccgaacatga acggatacga gctaaccgcg gagctacggc gccaagggtt ccggcagccg 1860
atcatcggcg cgacggcgaa cgccatgcgt gaggagcgcg agcgctgcat gtccgccggg 1920
atgaacgatt gcctggtcaa accggtggat ctgaatgccc ttcagaactg cttgattaat 1980
attctcaagg tggatcgatg a 2001

Figure 6K

ORF1-11
SEQ ID NO:18

```
atggaggcgg aactggctcg cgcaaaatcc ctggcggatg ctgccaatga agccaagacg 60
ctgtttctcg ccaccatgag ccatgaaatc cgcacacctc tgtacggcat gcttggcacg 120
cttgagctgc ttgggcgtac cgagctgagt cggcagcagg ccggttacct aaaggcaatc 180
cagcattcct cgtcgaccct gctgcaactg atcagcgatg tgcttgacgt atccaagata 240
gaggccggcc aactggacct agagtgcgtg gaattctccc cgctggaatt gaccgaagag 300
gtcgtgcagt cgttcaccgg tgccgcgcag gccaaggggc tgcagttgta tacctgcctc 360
tctgcggagc tgccgctgcg catgcggggg gccgcggcgt cgatccggca gattctcaac 420
aacctgctga gcaacgcggt gaagttcacc gacaatggct atgtcaacgt ccacctgaag 480
gccagcgtgg tcgatgccga atgtgtgatg ctgacctggc aggtcaacga taccggcatg 540
gggatcaacg tcgaggatca gccgcgtctg ttcgaaccgt tctaccagat acgccgctcc 600
gagcatccgg tcgcaggcac gggcctcggc ttgtcgatca gccagcgcct ggcgcagcta 660
atgaatggca gtctgaaact ggtcagtgag ctggggttgg gcagcagctt tagcctcagg 720
cttccgcttg agcggatcgc gatgcaggct gagccgcagg acctagccgg gtgcgccgtc 780
caagtgctgg cgcctgtccg cgacctaacg gaatgcctgt gtggctggat ctcccgctgg 840
ggtggaaggg ccatggtcgc gacgccgagg tcgctggacg aggcggacgc gacctcgctg 900
ctggtcgaag tgttactgct ggaggggcg ccgatgttcg aagcatggcc aggatgccgg 960
gtggagcttt cccctcaggg tgatatggag ccgcaggcac agggccgcga ctggctgctc 1020
gggctcaaca acctggacgg cctgcatcgt gctctgggcc tggcccatgg gcgtctcgct 1080
gatccttcga cgccgccgat acggctggct ccgttgcgca atctaggtct ccgcgtccta 1140
gtggtggagg ataacgcgat caaccagttg atcttgaggg accagatgga agcgctgggc 1200
tgcagcgtgg agctgctctt cgatggtcgc gaggcgttgc tgcactgcca gacggcctgc 1260
ttcgacgtgg tgctcaccga tatcaacatg ccgaacatga acggatacga gctaaccgcg 1320
gagctacggc gccaagggtt ccggcagccg atcatcggcg cgacggcgaa cgccatgcgt 1380
gaggagcgcg agcgctgcat gtccgccggg atgaacgatt gcctggtcaa accggtggat 1440
ctgaatgccc ttcagaactg cttgattaat attctcaagg tggatcgatg a          1491
```

Figure 6L

ORF1-1
SEQ ID NO:19

```
Met Lys Leu Lys Asn Phe Leu Gln Pro Phe Asp Ser Gly Phe Ser Thr
 1               5                  10                  15
Pro Ser Ala Ala Leu Lys Leu Leu Arg Met Leu Gly Gly Ala Leu Met
            20                  25                  30
Leu Cys Val Leu Cys Ser Leu Ile Phe Ser Val Ser Met Val Leu Asn
        35                  40                  45
His Gln Val Ser Leu Ser Arg Gln Ala Met Asn Val Ala Met Tyr Glu
    50                  55                  60
Ala Gln Leu Tyr Phe Glu Gln Arg Glu Ala Leu Leu Asn His Leu Ser
65                  70                  75                  80
Gly Asn Val Val Pro Leu Ala Ala Gly Arg Ala Leu Val Asn Glu Ala
                85                  90                  95
Pro Asn Asn Val Ser Ile Leu Pro Leu Ser Asp Gly Gly Arg Gly Leu
            100                 105                 110
Leu Leu Thr Ala Arg Thr Leu Gly Asp Leu Arg Glu Lys Arg Leu Ala
        115                 120                 125
Leu Met Tyr Leu Val Asp Thr Asp Lys Gly Pro Leu Val Tyr Arg Leu
    130                 135                 140
Thr Ala Asp Gly Arg Pro Ser Ala Ala Ile Ser Ser Thr Ile Thr Lys
145                 150                 155                 160
Glu Val Tyr Arg Ala Leu Leu Ala Thr Pro Ser Ala Pro Val His Trp
                165                 170                 175
Val Thr Asp Gly Gly Thr Pro Gln Arg Leu Tyr Leu Phe Glu Ser Leu
            180                 185                 190
Gly Asp Glu Pro Gly Glu Gly Trp Leu Gly Leu Glu Ile Leu Gly Glu
        195                 200                 205
Asp Leu Asp Ser Met Leu Arg Arg Asn Asp Ala Gly Asn Tyr Met Leu
    210                 215                 220
Leu Asp Gln His Gly Gln Val Val Leu Ala Thr Asp Ala Glu Ala Leu
225                 230                 235                 240
Gly Ser Gly Ala Ser Arg Thr Leu Leu Arg Gly Asp Gly Phe Gly Phe
                245                 250                 255
Ile Gly Ala Gly Pro Leu Pro Gln His Met Val Leu Phe Gln His Val
            260                 265                 270
Gly Ser Ser Ser Trp Asp Leu Ile Tyr His Ile Gly Ile Gly Arg Leu
        275                 280                 285
Leu Leu Ala Leu Trp Leu Pro Leu Leu Leu Ala Ser Ala Leu Ala Leu
    290                 295                 300
Ala Val Gly Ile Leu Leu His Trp Leu Val Arg Ser Ile Glu Arg Arg
305                 310                 315                 320
Leu Ile Glu Pro Ala Lys Arg Arg Leu Glu Ala Leu Lys Glu Ser Glu
                325                 330                 335
Ala Phe Ser Arg Ala Val Ile Gln Ala Ala Pro Val Ala Leu Cys Val
            340                 345                 350
Leu Arg Arg Ala Asp Ala Ala Val Val Leu Glu Asn Pro Gln Ala Arg
        355                 360                 365
Gln Trp Leu Gly Asp Ser Glu Ala Ile Ala His Asp Ala Pro Arg Trp
    370                 375                 380
Ile Ser Gln Ala Phe Ala Gly Gly Val Lys Cys Ser Gly Glu Glu Leu
385                 390                 395                 400
Glu Thr Glu Ala Gly Leu His Leu His Leu Asn Tyr Thr Pro Thr Arg
                405                 410                 415
Tyr Asn Gly Glu Asp Val Leu Phe Cys Ala Phe Ser Glu Ile Ser Ala
            420                 425                 430
Arg Lys Arg Met Glu Ala Glu Leu Ala Arg Ala Lys Ser Leu Ala Asp
        435                 440                 445
Ala Ala Asn Glu Ala Lys Thr Leu Phe Leu Ala Thr Met Ser His Glu
    450                 455                 460
```

6L/1

```
Ile Arg Thr Pro Leu Tyr Gly Met Leu Gly Thr Leu Glu Leu Leu Gly
465                 470                 475                 480
Arg Thr Glu Leu Ser Arg Gln Gln Ala Gly Tyr Leu Lys Ala Ile Gln
                485                 490                 495
His Ser Ser Ser Thr Leu Leu Gln Leu Ile Ser Asp Val Leu Asp Val
            500                 505                 510
Ser Lys Ile Glu Ala Gly Gln Leu Asp Leu Glu Cys Val Glu Phe Ser
        515                 520                 525
Pro Leu Glu Leu Thr Glu Glu Val Val Gln Ser Phe Thr Gly Ala Ala
    530                 535                 540
Gln Ala Lys Gly Leu Gln Leu Tyr Thr Cys Leu Ser Ala Glu Leu Pro
545                 550                 555                 560
Leu Arg Met Arg Gly Ala Ala Ala Ser Ile Arg Gln Ile Leu Asn Asn
                565                 570                 575
Leu Leu Ser Asn Ala Val Lys Phe Thr Asp Asn Gly Tyr Val Asn Val
            580                 585                 590
His Leu Lys Ala Ser Val Val Asp Ala Glu Cys Val Met Leu Thr Trp
        595                 600                 605
Gln Val Asn Asp Thr Gly Met Gly Ile Asn Val Glu Asp Gln Pro Arg
    610                 615                 620
Leu Phe Glu Pro Phe Tyr Gln Ile Arg Arg Ser Glu His Pro Val Ala
625                 630                 635                 640
Gly Thr Gly Leu Gly Leu Ser Ile Ser Gln Arg Leu Ala Gln Leu Met
                645                 650                 655
Asn Gly Ser Leu Lys Leu Val Ser Glu Leu Gly Leu Gly Ser Ser Phe
            660                 665                 670
Ser Leu Arg Leu Pro Leu Glu Arg Ile Ala Met Gln Ala Glu Pro Gln
        675                 680                 685
Asp Leu Ala Gly Cys Ala Val Gln Val Leu Ala Pro Val Arg Asp Leu
    690                 695                 700
Thr Glu Cys Leu Cys Gly Trp Ile Ser Arg Trp Gly Gly Arg Ala Met
705                 710                 715                 720
Val Ala Thr Pro Arg Ser Leu Asp Glu Ala Asp Ala Thr Ser Leu Leu
                725                 730                 735
Val Glu Val Leu Leu Leu Glu Gly Ala Pro Met Phe Glu Ala Trp Pro
            740                 745                 750
Gly Cys Arg Val Glu Leu Ser Pro Gln Gly Asp Met Glu Pro Gln Ala
        755                 760                 765
Gln Gly Arg Asp Trp Leu Leu Gly Leu Asn Asn Leu Asp Gly Leu His
    770                 775                 780
Arg Ala Leu Gly Leu Ala His Gly Arg Leu Ala Asp Pro Ser Thr Pro
785                 790                 795                 800
Pro Ile Arg Leu Ala Pro Leu Arg Asn Leu Gly Leu Arg Val Leu Val
                805                 810                 815
Val Glu Asp Asn Ala Ile Asn Gln Leu Ile Leu Arg Asp Gln Met Glu
            820                 825                 830
Ala Leu Gly Cys Ser Val Glu Leu Leu Phe Asp Gly Arg Glu Ala Leu
        835                 840                 845
Leu His Cys Gln Thr Ala Cys Phe Asp Val Val Leu Thr Asp Ile Asn
    850                 855                 860
Met Pro Asn Met Asn Gly Tyr Glu Leu Thr Ala Glu Leu Arg Arg Gln
865                 870                 875                 880
Gly Phe Arg Gln Pro Ile Ile Gly Ala Thr Ala Asn Ala Met Arg Glu
                885                 890                 895
Glu Arg Glu Arg Cys Met Ser Ala Gly Met Asn Asp Cys Leu Val Lys
            900                 905                 910
Pro Val Asp Leu Asn Ala Leu Gln Asn Cys Leu Ile Asn Ile Leu Lys
        915                 920                 925
Val Asp Arg
    930
```

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Figure 6M

ORF1-2
SEQ ID NO:20

```
Met Leu Gly Gly Ala Leu Met Leu Cys Val Leu Cys Ser Leu Ile Phe
 1               5                  10                  15
Ser Val Ser Met Val Leu Asn His Gln Val Ser Leu Ser Arg Gln Ala
            20                  25                  30
Met Asn Val Ala Met Tyr Glu Ala Gln Leu Tyr Phe Glu Gln Arg Glu
        35                  40                  45
Ala Leu Leu Asn His Leu Ser Gly Asn Val Val Pro Leu Ala Ala Gly
    50                  55                  60
Arg Ala Leu Val Asn Glu Ala Pro Asn Asn Val Ser Ile Leu Pro Leu
65                  70                  75                  80
Ser Asp Gly Gly Arg Gly Leu Leu Leu Thr Ala Arg Thr Leu Gly Asp
                85                  90                  95
Leu Arg Glu Lys Arg Leu Ala Leu Met Tyr Leu Val Asp Thr Asp Lys
            100                 105                 110
Gly Pro Leu Val Tyr Arg Leu Thr Ala Asp Gly Arg Pro Ser Ala Ala
        115                 120                 125
Ile Ser Ser Thr Ile Thr Lys Glu Val Tyr Arg Ala Leu Leu Ala Thr
    130                 135                 140
Pro Ser Ala Pro Val His Trp Val Thr Asp Gly Gly Thr Pro Gln Arg
145                 150                 155                 160
Leu Tyr Leu Phe Glu Ser Leu Gly Asp Glu Pro Gly Glu Gly Trp Leu
                165                 170                 175
Gly Leu Glu Ile Leu Gly Glu Asp Leu Asp Ser Met Leu Arg Arg Asn
            180                 185                 190
Asp Ala Gly Asn Tyr Met Leu Leu Asp Gln His Gly Gln Val Val Leu
        195                 200                 205
Ala Thr Asp Ala Glu Ala Leu Gly Ser Gly Ala Ser Arg Thr Leu Leu
    210                 215                 220
Arg Gly Asp Gly Phe Gly Phe Ile Gly Ala Gly Pro Leu Pro Gln His
225                 230                 235                 240
Met Val Leu Phe Gln His Val Gly Ser Ser Ser Trp Asp Leu Ile Tyr
                245                 250                 255
His Ile Gly Ile Gly Arg Leu Leu Leu Ala Leu Trp Leu Pro Leu Leu
            260                 265                 270
Leu Ala Ser Ala Leu Ala Leu Ala Val Gly Ile Leu Leu His Trp Leu
        275                 280                 285
Val Arg Ser Ile Glu Arg Arg Leu Ile Glu Pro Ala Lys Arg Arg Leu
    290                 295                 300
Glu Ala Leu Lys Glu Ser Glu Ala Phe Ser Arg Ala Val Ile Gln Ala
305                 310                 315                 320
Ala Pro Val Ala Leu Cys Val Leu Arg Arg Ala Asp Ala Ala Val Val
                325                 330                 335
Leu Glu Asn Pro Gln Ala Arg Gln Trp Leu Gly Asp Ser Glu Ala Ile
            340                 345                 350
Ala His Asp Ala Pro Arg Trp Ile Ser Gln Ala Phe Ala Gly Gly Val
        355                 360                 365
Lys Cys Ser Gly Glu Glu Leu Glu Thr Glu Ala Gly Leu His Leu His
    370                 375                 380
Leu Asn Tyr Thr Pro Thr Arg Tyr Asn Gly Glu Asp Val Leu Phe Cys
385                 390                 395                 400
Ala Phe Ser Glu Ile Ser Ala Arg Lys Arg Met Glu Ala Glu Leu Ala
                405                 410                 415
Arg Ala Lys Ser Leu Ala Asp Ala Ala Asn Glu Ala Lys Thr Leu Phe
            420                 425                 430
Leu Ala Thr Met Ser His Glu Ile Arg Thr Pro Leu Tyr Gly Met Leu
        435                 440                 445
Gly Thr Leu Glu Leu Leu Gly Arg Thr Glu Leu Ser Arg Gln Gln Ala
    450                 455                 460
```

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```
Gly Tyr Leu Lys Ala Ile Gln His Ser Ser Ser Thr Leu Leu Gln Leu
465                 470                 475                 480
Ile Ser Asp Val Leu Asp Val Ser Lys Ile Glu Ala Gly Gln Leu Asp
                485                 490                 495
Leu Glu Cys Val Glu Phe Ser Pro Leu Glu Leu Thr Glu Glu Val Val
            500                 505                 510
Gln Ser Phe Thr Gly Ala Ala Gln Ala Lys Gly Leu Gln Leu Tyr Thr
        515                 520                 525
Cys Leu Ser Ala Glu Leu Pro Leu Arg Met Arg Gly Ala Ala Ala Ser
    530                 535                 540
Ile Arg Gln Ile Leu Asn Asn Leu Leu Ser Asn Ala Val Lys Phe Thr
545                 550                 555                 560
Asp Asn Gly Tyr Val Asn Val His Leu Lys Ala Ser Val Val Asp Ala
                565                 570                 575
Glu Cys Val Met Leu Thr Trp Gln Val Asn Asp Thr Gly Met Gly Ile
            580                 585                 590
Asn Val Glu Asp Gln Pro Arg Leu Phe Glu Pro Phe Tyr Gln Ile Arg
        595                 600                 605
Arg Ser Glu His Pro Val Ala Gly Thr Gly Leu Gly Leu Ser Ile Ser
    610                 615                 620
Gln Arg Leu Ala Gln Leu Met Asn Gly Ser Leu Lys Leu Val Ser Glu
625                 630                 635                 640
Leu Gly Leu Gly Ser Ser Phe Ser Leu Arg Leu Pro Leu Glu Arg Ile
                645                 650                 655
Ala Met Gln Ala Glu Pro Gln Asp Leu Ala Gly Cys Ala Val Gln Val
            660                 665                 670
Leu Ala Pro Val Arg Asp Leu Thr Glu Cys Leu Cys Gly Trp Ile Ser
        675                 680                 685
Arg Trp Gly Gly Arg Ala Met Val Ala Thr Pro Arg Ser Leu Asp Glu
    690                 695                 700
Ala Asp Ala Thr Ser Leu Leu Val Glu Val Leu Leu Leu Glu Gly Ala
705                 710                 715                 720
Pro Met Phe Glu Ala Trp Pro Gly Cys Arg Val Glu Leu Ser Pro Gln
                725                 730                 735
Gly Asp Met Glu Pro Gln Ala Gln Gly Arg Asp Trp Leu Leu Gly Leu
            740                 745                 750
Asn Asn Leu Asp Gly Leu His Arg Ala Leu Gly Leu Ala His Gly Arg
        755                 760                 765
Leu Ala Asp Pro Ser Thr Pro Pro Ile Arg Leu Ala Pro Leu Arg Asn
    770                 775                 780
Leu Gly Leu Arg Val Leu Val Val Glu Asp Asn Ala Ile Asn Gln Leu
785                 790                 795                 800
Ile Leu Arg Asp Gln Met Glu Ala Leu Gly Cys Ser Val Glu Leu Leu
                805                 810                 815
Phe Asp Gly Arg Glu Ala Leu Leu His Cys Gln Thr Ala Cys Phe Asp
            820                 825                 830
Val Val Leu Thr Asp Ile Asn Met Pro Asn Met Asn Gly Tyr Glu Leu
        835                 840                 845
Thr Ala Glu Leu Arg Arg Gln Gly Phe Arg Gln Pro Ile Ile Gly Ala
    850                 855                 860
Thr Ala Asn Ala Met Arg Glu Glu Arg Glu Arg Cys Met Ser Ala Gly
865                 870                 875                 880
Met Asn Asp Cys Leu Val Lys Pro Val Asp Leu Asn Ala Leu Gln Asn
                885                 890                 895
Cys Leu Ile Asn Ile Leu Lys Val Asp Arg
            900                 905
```

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Figure 6N

SEQ ID NO:21
ORF1-3

```
Met Leu Cys Val Leu Cys Ser Leu Ile Phe Ser Val Ser Met Val Leu
 1               5                  10                  15
Asn His Gln Val Ser Leu Ser Arg Gln Ala Met Asn Val Ala Met Tyr
            20                  25                  30
Glu Ala Gln Leu Tyr Phe Glu Gln Arg Glu Ala Leu Leu Asn His Leu
        35                  40                  45
Ser Gly Asn Val Val Pro Leu Ala Ala Gly Arg Ala Leu Val Asn Glu
    50                  55                  60
Ala Pro Asn Asn Val Ser Ile Leu Pro Leu Ser Asp Gly Gly Arg Gly
65                  70                  75                  80
Leu Leu Leu Thr Ala Arg Thr Leu Gly Asp Leu Arg Glu Lys Arg Leu
                85                  90                  95
Ala Leu Met Tyr Leu Val Asp Thr Asp Lys Gly Pro Leu Val Tyr Arg
            100                 105                 110
Leu Thr Ala Asp Gly Arg Pro Ser Ala Ala Ile Ser Ser Thr Ile Thr
        115                 120                 125
Lys Glu Val Tyr Arg Ala Leu Leu Ala Thr Pro Ser Ala Pro Val His
    130                 135                 140
Trp Val Thr Asp Gly Gly Thr Pro Gln Arg Leu Tyr Leu Phe Glu Ser
145                 150                 155                 160
Leu Gly Asp Glu Pro Gly Glu Gly Trp Leu Gly Leu Glu Ile Leu Gly
                165                 170                 175
Glu Asp Leu Asp Ser Met Leu Arg Arg Asn Asp Ala Gly Asn Tyr Met
            180                 185                 190
Leu Leu Asp Gln His Gly Gln Val Val Leu Ala Thr Asp Ala Glu Ala
        195                 200                 205
Leu Gly Ser Gly Ala Ser Arg Thr Leu Leu Arg Gly Asp Gly Phe Gly
    210                 215                 220
Phe Ile Gly Ala Gly Pro Leu Pro Gln His Met Val Leu Phe Gln His
225                 230                 235                 240
Val Gly Ser Ser Ser Trp Asp Leu Ile Tyr His Ile Gly Ile Gly Arg
                245                 250                 255
Leu Leu Leu Ala Leu Trp Leu Pro Leu Leu Leu Ala Ser Ala Leu Ala
            260                 265                 270
Leu Ala Val Gly Ile Leu Leu His Trp Leu Val Arg Ser Ile Glu Arg
        275                 280                 285
Arg Leu Ile Glu Pro Ala Lys Arg Arg Leu Glu Ala Leu Lys Glu Ser
    290                 295                 300
Glu Ala Phe Ser Arg Ala Val Ile Gln Ala Ala Pro Val Ala Leu Cys
305                 310                 315                 320
Val Leu Arg Arg Ala Asp Ala Ala Val Val Leu Glu Asn Pro Gln Ala
                325                 330                 335
Arg Gln Trp Leu Gly Asp Ser Glu Ala Ile Ala His Asp Ala Pro Arg
            340                 345                 350
Trp Ile Ser Gln Ala Phe Ala Gly Gly Val Lys Cys Ser Gly Glu Glu
        355                 360                 365
Leu Glu Thr Glu Ala Gly Leu His Leu His Leu Asn Tyr Thr Pro Thr
    370                 375                 380
Arg Tyr Asn Gly Glu Asp Val Leu Phe Cys Ala Phe Ser Glu Ile Ser
385                 390                 395                 400
Ala Arg Lys Arg Met Glu Ala Glu Leu Ala Arg Ala Lys Ser Leu Ala
                405                 410                 415
Asp Ala Ala Asn Glu Ala Lys Thr Leu Phe Leu Ala Thr Met Ser His
            420                 425                 430
Glu Ile Arg Thr Pro Leu Tyr Gly Met Leu Gly Thr Leu Glu Leu Leu
        435                 440                 445
Gly Arg Thr Glu Leu Ser Arg Gln Gln Ala Gly Tyr Leu Lys Ala Ile
    450                 455                 460
```

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```
Gln His Ser Ser Ser Thr Leu Leu Gln Leu Ile Ser Asp Val Leu Asp
465                 470                 475                 480
Val Ser Lys Ile Glu Ala Gly Gln Leu Asp Leu Glu Cys Val Glu Phe
                485                 490                 495
Ser Pro Leu Glu Leu Thr Glu Glu Val Val Gln Ser Phe Thr Gly Ala
            500                 505                 510
Ala Gln Ala Lys Gly Leu Gln Leu Tyr Thr Cys Leu Ser Ala Glu Leu
        515                 520                 525
Pro Leu Arg Met Arg Gly Ala Ala Ala Ser Ile Arg Gln Ile Leu Asn
    530                 535                 540
Asn Leu Leu Ser Asn Ala Val Lys Phe Thr Asp Asn Gly Tyr Val Asn
545                 550                 555                 560
Val His Leu Lys Ala Ser Val Val Asp Ala Glu Cys Val Met Leu Thr
                565                 570                 575
Trp Gln Val Asn Asp Thr Gly Met Gly Ile Asn Val Glu Asp Gln Pro
            580                 585                 590
Arg Leu Phe Glu Pro Phe Tyr Gln Ile Arg Arg Ser Glu His Pro Val
        595                 600                 605
Ala Gly Thr Gly Leu Gly Leu Ser Ile Ser Gln Arg Leu Ala Gln Leu
    610                 615                 620
Met Asn Gly Ser Leu Lys Leu Val Ser Glu Leu Gly Leu Gly Ser Ser
625                 630                 635                 640
Phe Ser Leu Arg Leu Pro Leu Glu Arg Ile Ala Met Gln Ala Glu Pro
                645                 650                 655
Gln Asp Leu Ala Gly Cys Ala Val Gln Val Leu Ala Pro Val Arg Asp
            660                 665                 670
Leu Thr Glu Cys Leu Cys Gly Trp Ile Ser Arg Trp Gly Gly Arg Ala
        675                 680                 685
Met Val Ala Thr Pro Arg Ser Leu Asp Glu Ala Asp Ala Thr Ser Leu
    690                 695                 700
Leu Val Glu Val Leu Leu Leu Glu Gly Ala Pro Met Phe Glu Ala Trp
705                 710                 715                 720
Pro Gly Cys Arg Val Glu Leu Ser Pro Gln Gly Asp Met Glu Pro Gln
                725                 730                 735
Ala Gln Gly Arg Asp Trp Leu Leu Gly Leu Asn Asn Leu Asp Gly Leu
            740                 745                 750
His Arg Ala Leu Gly Leu Ala His Gly Arg Leu Ala Asp Pro Ser Thr
        755                 760                 765
Pro Pro Ile Arg Leu Ala Pro Leu Arg Asn Leu Gly Leu Arg Val Leu
    770                 775                 780
Val Val Glu Asp Asn Ala Ile Asn Gln Leu Ile Leu Arg Asp Gln Met
785                 790                 795                 800
Glu Ala Leu Gly Cys Ser Val Glu Leu Leu Phe Asp Gly Arg Glu Ala
                805                 810                 815
Leu Leu His Cys Gln Thr Ala Cys Phe Asp Val Val Leu Thr Asp Ile
            820                 825                 830
Asn Met Pro Asn Met Asn Gly Tyr Glu Leu Thr Ala Glu Leu Arg Arg
        835                 840                 845
Gln Gly Phe Arg Gln Pro Ile Ile Gly Ala Thr Ala Asn Ala Met Arg
    850                 855                 860
Glu Glu Arg Glu Arg Cys Met Ser Ala Gly Met Asn Asp Cys Leu Val
865                 870                 875                 880
Lys Pro Val Asp Leu Asn Ala Leu Gln Asn Cys Leu Ile Asn Ile Leu
                885                 890                 895
Lys Val Asp Arg
            900
```

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Figure 60

ORF1-4
SEQ ID NO:22

```
Met Val Leu Asn His Gln Val Ser Leu Ser Arg Gln Ala Met Asn Val
 1               5                  10                  15
Ala Met Tyr Glu Ala Gln Leu Tyr Phe Glu Gln Arg Glu Ala Leu Leu
            20                  25                  30
Asn His Leu Ser Gly Asn Val Val Pro Leu Ala Ala Gly Arg Ala Leu
        35                  40                  45
Val Asn Glu Ala Pro Asn Asn Val Ser Ile Leu Pro Leu Ser Asp Gly
    50                  55                  60
Gly Arg Gly Leu Leu Leu Thr Ala Arg Thr Leu Gly Asp Leu Arg Glu
65                  70                  75                  80
Lys Arg Leu Ala Leu Met Tyr Leu Val Asp Thr Asp Lys Gly Pro Leu
                85                  90                  95
Val Tyr Arg Leu Thr Ala Asp Gly Arg Pro Ser Ala Ala Ile Ser Ser
            100                 105                 110
Thr Ile Thr Lys Glu Val Tyr Arg Ala Leu Leu Ala Thr Pro Ser Ala
        115                 120                 125
Pro Val His Trp Val Thr Asp Gly Gly Thr Pro Gln Arg Leu Tyr Leu
    130                 135                 140
Phe Glu Ser Leu Gly Asp Glu Pro Gly Glu Gly Trp Leu Gly Leu Glu
145                 150                 155                 160
Ile Leu Gly Glu Asp Leu Asp Ser Met Leu Arg Arg Asn Asp Ala Gly
                165                 170                 175
Asn Tyr Met Leu Leu Asp Gln His Gly Gln Val Val Leu Ala Thr Asp
            180                 185                 190
Ala Glu Ala Leu Gly Ser Gly Ala Ser Arg Thr Leu Leu Arg Gly Asp
        195                 200                 205
Gly Phe Gly Phe Ile Gly Ala Gly Pro Leu Pro Gln His Met Val Leu
    210                 215                 220
Phe Gln His Val Gly Ser Ser Ser Trp Asp Leu Ile Tyr His Ile Gly
225                 230                 235                 240
Ile Gly Arg Leu Leu Leu Ala Leu Trp Leu Pro Leu Leu Leu Ala Ser
                245                 250                 255
Ala Leu Ala Leu Ala Val Gly Ile Leu Leu His Trp Leu Val Arg Ser
            260                 265                 270
Ile Glu Arg Arg Leu Ile Glu Pro Ala Lys Arg Arg Leu Glu Ala Leu
        275                 280                 285
Lys Glu Ser Glu Ala Phe Ser Arg Ala Val Ile Gln Ala Ala Pro Val
    290                 295                 300
Ala Leu Cys Val Leu Arg Arg Ala Asp Ala Ala Val Val Leu Glu Asn
305                 310                 315                 320
Pro Gln Ala Arg Gln Trp Leu Gly Asp Ser Glu Ala Ile Ala His Asp
                325                 330                 335
Ala Pro Arg Trp Ile Ser Gln Ala Phe Ala Gly Gly Val Lys Cys Ser
            340                 345                 350
Gly Glu Glu Leu Glu Thr Glu Ala Gly Leu His Leu His Leu Asn Tyr
        355                 360                 365
Thr Pro Thr Arg Tyr Asn Gly Glu Asp Val Leu Phe Cys Ala Phe Ser
    370                 375                 380
Glu Ile Ser Ala Arg Lys Arg Met Glu Ala Glu Leu Ala Arg Ala Lys
385                 390                 395                 400
Ser Leu Ala Asp Ala Ala Asn Glu Ala Lys Thr Leu Phe Leu Ala Thr
                405                 410                 415
Met Ser His Glu Ile Arg Thr Pro Leu Tyr Gly Met Leu Gly Thr Leu
            420                 425                 430
Glu Leu Leu Gly Arg Thr Glu Leu Ser Arg Gln Gln Ala Gly Tyr Leu
        435                 440                 445
Lys Ala Ile Gln His Ser Ser Ser Thr Leu Leu Gln Leu Ile Ser Asp
    450                 455                 460
```

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```
Val Leu Asp Val Ser Lys Ile Glu Ala Gly Gln Leu Asp Leu Glu Cys
465                 470                 475                 480
Val Glu Phe Ser Pro Leu Glu Leu Thr Glu Glu Val Val Gln Ser Phe
                485                 490                 495
Thr Gly Ala Ala Gln Ala Lys Gly Leu Gln Leu Tyr Thr Cys Leu Ser
            500                 505                 510
Ala Glu Leu Pro Leu Arg Met Arg Gly Ala Ala Ala Ser Ile Arg Gln
        515                 520                 525
Ile Leu Asn Asn Leu Leu Ser Asn Ala Val Lys Phe Thr Asp Asn Gly
    530                 535                 540
Tyr Val Asn Val His Leu Lys Ala Ser Val Val Asp Ala Glu Cys Val
545                 550                 555                 560
Met Leu Thr Trp Gln Val Asn Asp Thr Gly Met Gly Ile Asn Val Glu
                565                 570                 575
Asp Gln Pro Arg Leu Phe Glu Pro Phe Tyr Gln Ile Arg Arg Ser Glu
            580                 585                 590
His Pro Val Ala Gly Thr Gly Leu Gly Leu Ser Ile Ser Gln Arg Leu
        595                 600                 605
Ala Gln Leu Met Asn Gly Ser Leu Lys Leu Val Ser Glu Leu Gly Leu
    610                 615                 620
Gly Ser Ser Phe Ser Leu Arg Leu Pro Leu Glu Arg Ile Ala Met Gln
625                 630                 635                 640
Ala Glu Pro Gln Asp Leu Ala Gly Cys Ala Val Gln Val Leu Ala Pro
                645                 650                 655
Val Arg Asp Leu Thr Glu Cys Leu Cys Gly Trp Ile Ser Arg Trp Gly
            660                 665                 670
Gly Arg Ala Met Val Ala Thr Pro Arg Ser Leu Asp Glu Ala Asp Ala
        675                 680                 685
Thr Ser Leu Leu Val Glu Val Leu Leu Leu Glu Gly Ala Pro Met Phe
    690                 695                 700
Glu Ala Trp Pro Gly Cys Arg Val Glu Leu Ser Pro Gln Gly Asp Met
705                 710                 715                 720
Glu Pro Gln Ala Gln Gly Arg Asp Trp Leu Leu Gly Leu Asn Asn Leu
                725                 730                 735
Asp Gly Leu His Arg Ala Leu Gly Leu Ala His Gly Arg Leu Ala Asp
            740                 745                 750
Pro Ser Thr Pro Pro Ile Arg Leu Ala Pro Leu Arg Asn Leu Gly Leu
        755                 760                 765
Arg Val Leu Val Val Glu Asp Asn Ala Ile Asn Gln Leu Ile Leu Arg
    770                 775                 780
Asp Gln Met Glu Ala Leu Gly Cys Ser Val Glu Leu Leu Phe Asp Gly
785                 790                 795                 800
Arg Glu Ala Leu Leu His Cys Gln Thr Ala Cys Phe Asp Val Val Leu
                805                 810                 815
Thr Asp Ile Asn Met Pro Asn Met Asn Gly Tyr Glu Leu Thr Ala Glu
            820                 825                 830
Leu Arg Arg Gln Gly Phe Arg Gln Pro Ile Ile Gly Ala Thr Ala Asn
        835                 840                 845
Ala Met Arg Glu Glu Arg Glu Arg Cys Met Ser Ala Gly Met Asn Asp
    850                 855                 860
Cys Leu Val Lys Pro Val Asp Leu Asn Ala Leu Gln Asn Cys Leu Ile
865                 870                 875                 880
Asn Ile Leu Lys Val Asp Arg
                885
```

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Figure 6P

ORF1-5
SEQ ID NO:23

```
Met Asn Val Ala Met Tyr Glu Ala Gln Leu Tyr Phe Glu Gln Arg Glu
 1               5                  10                  15
Ala Leu Leu Asn His Leu Ser Gly Asn Val Val Pro Leu Ala Ala Gly
            20                  25                  30
Arg Ala Leu Val Asn Glu Ala Pro Asn Asn Val Ser Ile Leu Pro Leu
        35                  40                  45
Ser Asp Gly Gly Arg Gly Leu Leu Leu Thr Ala Arg Thr Leu Gly Asp
    50                  55                  60
Leu Arg Glu Lys Arg Leu Ala Leu Met Tyr Leu Val Asp Thr Asp Lys
65                  70                  75                  80
Gly Pro Leu Val Tyr Arg Leu Thr Ala Asp Gly Arg Pro Ser Ala Ala
                85                  90                  95
Ile Ser Ser Thr Ile Thr Lys Glu Val Tyr Arg Ala Leu Leu Ala Thr
            100                 105                 110
Pro Ser Ala Pro Val His Trp Val Thr Asp Gly Gly Thr Pro Gln Arg
        115                 120                 125
Leu Tyr Leu Phe Glu Ser Leu Gly Asp Glu Pro Gly Glu Gly Trp Leu
    130                 135                 140
Gly Leu Glu Ile Leu Gly Glu Asp Leu Asp Ser Met Leu Arg Arg Asn
145                 150                 155                 160
Asp Ala Gly Asn Tyr Met Leu Leu Asp Gln His Gly Gln Val Val Leu
                165                 170                 175
Ala Thr Asp Ala Glu Ala Leu Gly Ser Gly Ala Ser Arg Thr Leu Leu
            180                 185                 190
Arg Gly Asp Gly Phe Gly Phe Ile Gly Ala Gly Pro Leu Pro Gln His
        195                 200                 205
Met Val Leu Phe Gln His Val Gly Ser Ser Ser Trp Asp Leu Ile Tyr
    210                 215                 220
His Ile Gly Ile Gly Arg Leu Leu Leu Ala Leu Trp Leu Pro Leu Leu
225                 230                 235                 240
Leu Ala Ser Ala Leu Ala Leu Ala Val Gly Ile Leu Leu His Trp Leu
                245                 250                 255
Val Arg Ser Ile Glu Arg Arg Leu Ile Glu Pro Ala Lys Arg Arg Leu
            260                 265                 270
Glu Ala Leu Lys Glu Ser Glu Ala Phe Ser Arg Ala Val Ile Gln Ala
        275                 280                 285
Ala Pro Val Ala Leu Cys Val Leu Arg Arg Ala Asp Ala Ala Val Val
    290                 295                 300
Leu Glu Asn Pro Gln Ala Arg Gln Trp Leu Gly Asp Ser Glu Ala Ile
305                 310                 315                 320
Ala His Asp Ala Pro Arg Trp Ile Ser Gln Ala Phe Ala Gly Gly Val
                325                 330                 335
Lys Cys Ser Gly Glu Glu Leu Glu Thr Glu Ala Gly Leu His Leu His
            340                 345                 350
Leu Asn Tyr Thr Pro Thr Arg Tyr Asn Gly Glu Asp Val Leu Phe Cys
        355                 360                 365
Ala Phe Ser Glu Ile Ser Ala Arg Lys Arg Met Glu Ala Glu Leu Ala
    370                 375                 380
Arg Ala Lys Ser Leu Ala Asp Ala Ala Asn Glu Ala Lys Thr Leu Phe
385                 390                 395                 400
Leu Ala Thr Met Ser His Glu Ile Arg Thr Pro Leu Tyr Gly Met Leu
                405                 410                 415
Gly Thr Leu Glu Leu Leu Gly Arg Thr Glu Leu Ser Arg Gln Gln Ala
            420                 425                 430
Gly Tyr Leu Lys Ala Ile Gln His Ser Ser Ser Thr Leu Leu Gln Leu
        435                 440                 445
Ile Ser Asp Val Leu Asp Val Ser Lys Ile Glu Ala Gly Gln Leu Asp
    450                 455                 460
```

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```
Leu Glu Cys Val Glu Phe Ser Pro Leu Glu Leu Thr Glu Glu Val Val
465                 470                 475                 480
Gln Ser Phe Thr Gly Ala Ala Gln Ala Lys Gly Leu Gln Leu Tyr Thr
                485                 490                 495
Cys Leu Ser Ala Glu Leu Pro Leu Arg Met Arg Gly Ala Ala Ala Ser
            500                 505                 510
Ile Arg Gln Ile Leu Asn Asn Leu Leu Ser Asn Ala Val Lys Phe Thr
        515                 520                 525
Asp Asn Gly Tyr Val Asn Val His Leu Lys Ala Ser Val Val Asp Ala
    530                 535                 540
Glu Cys Val Met Leu Thr Trp Gln Val Asn Asp Thr Gly Met Gly Ile
545                 550                 555                 560
Asn Val Glu Asp Gln Pro Arg Leu Phe Glu Pro Phe Tyr Gln Ile Arg
                565                 570                 575
Arg Ser Glu His Pro Val Ala Gly Thr Gly Leu Gly Leu Ser Ile Ser
            580                 585                 590
Gln Arg Leu Ala Gln Leu Met Asn Gly Ser Leu Lys Leu Val Ser Glu
        595                 600                 605
Leu Gly Leu Gly Ser Ser Phe Ser Leu Arg Leu Pro Leu Glu Arg Ile
    610                 615                 620
Ala Met Gln Ala Glu Pro Gln Asp Leu Ala Gly Cys Ala Val Gln Val
625                 630                 635                 640
Leu Ala Pro Val Arg Asp Leu Thr Glu Cys Leu Cys Gly Trp Ile Ser
                645                 650                 655
Arg Trp Gly Gly Arg Ala Met Val Ala Thr Pro Arg Ser Leu Asp Glu
            660                 665                 670
Ala Asp Ala Thr Ser Leu Leu Val Glu Val Leu Leu Leu Glu Gly Ala
        675                 680                 685
Pro Met Phe Glu Ala Trp Pro Gly Cys Arg Val Glu Leu Ser Pro Gln
    690                 695                 700
Gly Asp Met Glu Pro Gln Ala Gln Gly Arg Asp Trp Leu Leu Gly Leu
705                 710                 715                 720
Asn Asn Leu Asp Gly Leu His Arg Ala Leu Gly Leu Ala His Gly Arg
                725                 730                 735
Leu Ala Asp Pro Ser Thr Pro Pro Ile Arg Leu Ala Pro Leu Arg Asn
            740                 745                 750
Leu Gly Leu Arg Val Leu Val Val Glu Asp Asn Ala Ile Asn Gln Leu
        755                 760                 765
Ile Leu Arg Asp Gln Met Glu Ala Leu Gly Cys Ser Val Glu Leu Leu
    770                 775                 780
Phe Asp Gly Arg Glu Ala Leu Leu His Cys Gln Thr Ala Cys Phe Asp
785                 790                 795                 800
Val Val Leu Thr Asp Ile Asn Met Pro Asn Met Asn Gly Tyr Glu Leu
                805                 810                 815
Thr Ala Glu Leu Arg Arg Gln Gly Phe Arg Gln Pro Ile Ile Gly Ala
            820                 825                 830
Thr Ala Asn Ala Met Arg Glu Glu Arg Glu Arg Cys Met Ser Ala Gly
        835                 840                 845
Met Asn Asp Cys Leu Val Lys Pro Val Asp Leu Asn Ala Leu Gln Asn
    850                 855                 860
Cys Leu Ile Asn Ile Leu Lys Val Asp Arg
865                 870
```

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Figure 6Q

ORF1-6
SEQ ID NO:24

```
Met Tyr Glu Ala Gln Leu Tyr Phe Glu Gln Arg Glu Ala Leu Leu Asn
 1               5                  10                  15
His Leu Ser Gly Asn Val Val Pro Leu Ala Ala Gly Arg Ala Leu Val
            20                  25                  30
Asn Glu Ala Pro Asn Asn Val Ser Ile Leu Pro Leu Ser Asp Gly Gly
        35                  40                  45
Arg Gly Leu Leu Leu Thr Ala Arg Thr Leu Gly Asp Leu Arg Glu Lys
    50                  55                  60
Arg Leu Ala Leu Met Tyr Leu Val Asp Thr Asp Lys Gly Pro Leu Val
65                  70                  75                  80
Tyr Arg Leu Thr Ala Asp Gly Arg Pro Ser Ala Ala Ile Ser Ser Thr
                85                  90                  95
Ile Thr Lys Glu Val Tyr Arg Ala Leu Leu Ala Thr Pro Ser Ala Pro
            100                 105                 110
Val His Trp Val Thr Asp Gly Gly Thr Pro Gln Arg Leu Tyr Leu Phe
        115                 120                 125
Glu Ser Leu Gly Asp Glu Pro Gly Glu Gly Trp Leu Gly Leu Glu Ile
    130                 135                 140
Leu Gly Glu Asp Leu Asp Ser Met Leu Arg Arg Asn Asp Ala Gly Asn
145                 150                 155                 160
Tyr Met Leu Leu Asp Gln His Gly Gln Val Val Leu Ala Thr Asp Ala
                165                 170                 175
Glu Ala Leu Gly Ser Gly Ala Ser Arg Thr Leu Leu Arg Gly Asp Gly
            180                 185                 190
Phe Gly Phe Ile Gly Ala Gly Pro Leu Pro Gln His Met Val Leu Phe
        195                 200                 205
Gln His Val Gly Ser Ser Ser Trp Asp Leu Ile Tyr His Ile Gly Ile
    210                 215                 220
Gly Arg Leu Leu Leu Ala Leu Trp Leu Pro Leu Leu Leu Ala Ser Ala
225                 230                 235                 240
Leu Ala Leu Ala Val Gly Ile Leu Leu His Trp Leu Val Arg Ser Ile
                245                 250                 255
Glu Arg Arg Leu Ile Glu Pro Ala Lys Arg Arg Leu Glu Ala Leu Lys
            260                 265                 270
Glu Ser Glu Ala Phe Ser Arg Ala Val Ile Gln Ala Ala Pro Val Ala
        275                 280                 285
Leu Cys Val Leu Arg Arg Ala Asp Ala Ala Val Val Leu Glu Asn Pro
    290                 295                 300
Gln Ala Arg Gln Trp Leu Gly Asp Ser Glu Ala Ile Ala His Asp Ala
305                 310                 315                 320
Pro Arg Trp Ile Ser Gln Ala Phe Ala Gly Gly Val Lys Cys Ser Gly
                325                 330                 335
Glu Glu Leu Glu Thr Glu Ala Gly Leu His Leu His Leu Asn Tyr Thr
            340                 345                 350
Pro Thr Arg Tyr Asn Gly Glu Asp Val Leu Phe Cys Ala Phe Ser Glu
        355                 360                 365
Ile Ser Ala Arg Lys Arg Met Glu Ala Glu Leu Ala Arg Ala Lys Ser
    370                 375                 380
Leu Ala Asp Ala Ala Asn Glu Ala Lys Thr Leu Phe Leu Ala Thr Met
385                 390                 395                 400
Ser His Glu Ile Arg Thr Pro Leu Tyr Gly Met Leu Gly Thr Leu Glu
                405                 410                 415
Leu Leu Gly Arg Thr Glu Leu Ser Arg Gln Gln Ala Gly Tyr Leu Lys
            420                 425                 430
Ala Ile Gln His Ser Ser Ser Thr Leu Leu Gln Leu Ile Ser Asp Val
        435                 440                 445
Leu Asp Val Ser Lys Ile Glu Ala Gly Gln Leu Asp Leu Glu Cys Val
    450                 455                 460
```

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```
Glu Phe Ser Pro Leu Glu Leu Thr Glu Glu Val Val Gln Ser Phe Thr
465                 470                 475                 480
Gly Ala Ala Gln Ala Lys Gly Leu Gln Leu Tyr Thr Cys Leu Ser Ala
                485                 490                 495
Glu Leu Pro Leu Arg Met Arg Gly Ala Ala Ala Ser Ile Arg Gln Ile
            500                 505                 510
Leu Asn Asn Leu Leu Ser Asn Ala Val Lys Phe Thr Asp Asn Gly Tyr
        515                 520                 525
Val Asn Val His Leu Lys Ala Ser Val Val Asp Ala Glu Cys Val Met
    530                 535                 540
Leu Thr Trp Gln Val Asn Asp Thr Gly Met Gly Ile Asn Val Glu Asp
545                 550                 555                 560
Gln Pro Arg Leu Phe Glu Pro Phe Tyr Gln Ile Arg Arg Ser Glu His
                565                 570                 575
Pro Val Ala Gly Thr Gly Leu Gly Leu Ser Ile Ser Gln Arg Leu Ala
            580                 585                 590
Gln Leu Met Asn Gly Ser Leu Lys Leu Val Ser Glu Leu Gly Leu Gly
        595                 600                 605
Ser Ser Phe Ser Leu Arg Leu Pro Leu Glu Arg Ile Ala Met Gln Ala
    610                 615                 620
Glu Pro Gln Asp Leu Ala Gly Cys Ala Val Gln Val Leu Ala Pro Val
625                 630                 635                 640
Arg Asp Leu Thr Glu Cys Leu Cys Gly Trp Ile Ser Arg Trp Gly Gly
                645                 650                 655
Arg Ala Met Val Ala Thr Pro Arg Ser Leu Asp Glu Ala Asp Ala Thr
            660                 665                 670
Ser Leu Leu Val Glu Val Leu Leu Leu Glu Gly Ala Pro Met Phe Glu
        675                 680                 685
Ala Trp Pro Gly Cys Arg Val Glu Leu Ser Pro Gln Gly Asp Met Glu
    690                 695                 700
Pro Gln Ala Gln Gly Arg Asp Trp Leu Leu Gly Leu Asn Asn Leu Asp
705                 710                 715                 720
Gly Leu His Arg Ala Leu Gly Leu Ala His Gly Arg Leu Ala Asp Pro
                725                 730                 735
Ser Thr Pro Pro Ile Arg Leu Ala Pro Leu Arg Asn Leu Gly Leu Arg
            740                 745                 750
Val Leu Val Val Glu Asp Asn Ala Ile Asn Gln Leu Ile Leu Arg Asp
        755                 760                 765
Gln Met Glu Ala Leu Gly Cys Ser Val Glu Leu Leu Phe Asp Gly Arg
    770                 775                 780
Glu Ala Leu Leu His Cys Gln Thr Ala Cys Phe Asp Val Val Leu Thr
785                 790                 795                 800
Asp Ile Asn Met Pro Asn Met Asn Gly Tyr Glu Leu Thr Ala Glu Leu
                805                 810                 815
Arg Arg Gln Gly Phe Arg Gln Pro Ile Ile Gly Ala Thr Ala Asn Ala
            820                 825                 830
Met Arg Glu Glu Arg Glu Arg Cys Met Ser Ala Gly Met Asn Asp Cys
        835                 840                 845
Leu Val Lys Pro Val Asp Leu Asn Ala Leu Gln Asn Cys Leu Ile Asn
    850                 855                 860
Ile Leu Lys Val Asp Arg
865                 870
```

6Q/2

Figure 6R

ORF1-7
SEQ ID NO:25

```
Met Tyr Leu Val Asp Thr Asp Lys Gly Pro Leu Val Tyr Arg Leu Thr
 1               5                  10                  15
Ala Asp Gly Arg Pro Ser Ala Ala Ile Ser Ser Thr Ile Thr Lys Glu
            20                  25                  30
Val Tyr Arg Ala Leu Leu Ala Thr Pro Ser Ala Pro Val His Trp Val
        35                  40                  45
Thr Asp Gly Gly Thr Pro Gln Arg Leu Tyr Leu Phe Glu Ser Leu Gly
    50                  55                  60
Asp Glu Pro Gly Glu Gly Trp Leu Gly Leu Glu Ile Leu Gly Glu Asp
65                  70                  75                  80
Leu Asp Ser Met Leu Arg Arg Asn Asp Ala Gly Asn Tyr Met Leu Leu
                85                  90                  95
Asp Gln His Gly Gln Val Val Leu Ala Thr Asp Ala Glu Ala Leu Gly
            100                 105                 110
Ser Gly Ala Ser Arg Thr Leu Leu Arg Gly Asp Gly Phe Gly Phe Ile
        115                 120                 125
Gly Ala Gly Pro Leu Pro Gln His Met Val Leu Phe Gln His Val Gly
    130                 135                 140
Ser Ser Ser Trp Asp Leu Ile Tyr His Ile Gly Ile Gly Arg Leu Leu
145                 150                 155                 160
Leu Ala Leu Trp Leu Pro Leu Leu Leu Ala Ser Ala Leu Ala Leu Ala
                165                 170                 175
Val Gly Ile Leu Leu His Trp Leu Val Arg Ser Ile Glu Arg Arg Leu
            180                 185                 190
Ile Glu Pro Ala Lys Arg Arg Leu Glu Ala Leu Lys Glu Ser Glu Ala
        195                 200                 205
Phe Ser Arg Ala Val Ile Gln Ala Ala Pro Val Ala Leu Cys Val Leu
    210                 215                 220
Arg Arg Ala Asp Ala Ala Val Val Leu Glu Asn Pro Gln Ala Arg Gln
225                 230                 235                 240
Trp Leu Gly Asp Ser Glu Ala Ile Ala His Asp Ala Pro Arg Trp Ile
                245                 250                 255
Ser Gln Ala Phe Ala Gly Gly Val Lys Cys Ser Gly Glu Glu Leu Glu
            260                 265                 270
Thr Glu Ala Gly Leu His Leu His Leu Asn Tyr Thr Pro Thr Arg Tyr
        275                 280                 285
Asn Gly Glu Asp Val Leu Phe Cys Ala Phe Ser Glu Ile Ser Ala Arg
    290                 295                 300
Lys Arg Met Glu Ala Glu Leu Ala Arg Ala Lys Ser Leu Ala Asp Ala
305                 310                 315                 320
Ala Asn Glu Ala Lys Thr Leu Phe Leu Ala Thr Met Ser His Glu Ile
                325                 330                 335
Arg Thr Pro Leu Tyr Gly Met Leu Gly Thr Leu Glu Leu Leu Gly Arg
            340                 345                 350
Thr Glu Leu Ser Arg Gln Gln Ala Gly Tyr Leu Lys Ala Ile Gln His
        355                 360                 365
Ser Ser Ser Thr Leu Leu Gln Leu Ile Ser Asp Val Leu Asp Val Ser
    370                 375                 380
Lys Ile Glu Ala Gly Gln Leu Asp Leu Glu Cys Val Glu Phe Ser Pro
385                 390                 395                 400
Leu Glu Leu Thr Glu Glu Val Val Gln Ser Phe Thr Gly Ala Ala Gln
                405                 410                 415
Ala Lys Gly Leu Gln Leu Tyr Thr Cys Leu Ser Ala Glu Leu Pro Leu
            420                 425                 430
Arg Met Arg Gly Ala Ala Ala Ser Ile Arg Gln Ile Leu Asn Asn Leu
        435                 440                 445
Leu Ser Asn Ala Val Lys Phe Thr Asp Asn Gly Tyr Val Asn Val His
    450                 455                 460
```

6R/1

```
Leu Lys Ala Ser Val Val Asp Ala Glu Cys Val Met Leu Thr Trp Gln
465                 470                 475                 480
Val Asn Asp Thr Gly Met Gly Ile Asn Val Glu Asp Gln Pro Arg Leu
                485                 490                 495
Phe Glu Pro Phe Tyr Gln Ile Arg Arg Ser Glu His Pro Val Ala Gly
            500                 505                 510
Thr Gly Leu Gly Leu Ser Ile Ser Gln Arg Leu Ala Gln Leu Met Asn
        515                 520                 525
Gly Ser Leu Lys Leu Val Ser Glu Leu Gly Leu Gly Ser Ser Phe Ser
    530                 535                 540
Leu Arg Leu Pro Leu Glu Arg Ile Ala Met Gln Ala Glu Pro Gln Asp
545                 550                 555                 560
Leu Ala Gly Cys Ala Val Gln Val Leu Ala Pro Val Arg Asp Leu Thr
                565                 570                 575
Glu Cys Leu Cys Gly Trp Ile Ser Arg Trp Gly Gly Arg Ala Met Val
            580                 585                 590
Ala Thr Pro Arg Ser Leu Asp Glu Ala Asp Ala Thr Ser Leu Leu Val
        595                 600                 605
Glu Val Leu Leu Leu Glu Gly Ala Pro Met Phe Glu Ala Trp Pro Gly
    610                 615                 620
Cys Arg Val Glu Leu Ser Pro Gln Gly Asp Met Glu Pro Gln Ala Gln
625                 630                 635                 640
Gly Arg Asp Trp Leu Leu Gly Leu Asn Asn Leu Asp Gly Leu His Arg
                645                 650                 655
Ala Leu Gly Leu Ala His Gly Arg Leu Ala Asp Pro Ser Thr Pro Pro
            660                 665                 670
Ile Arg Leu Ala Pro Leu Arg Asn Leu Gly Leu Arg Val Leu Val Val
        675                 680                 685
Glu Asp Asn Ala Ile Asn Gln Leu Ile Leu Arg Asp Gln Met Glu Ala
    690                 695                 700
Leu Gly Cys Ser Val Glu Leu Leu Phe Asp Gly Arg Glu Ala Leu Leu
705                 710                 715                 720
His Cys Gln Thr Ala Cys Phe Asp Val Val Leu Thr Asp Ile Asn Met
                725                 730                 735
Pro Asn Met Asn Gly Tyr Glu Leu Thr Ala Glu Leu Arg Arg Gln Gly
            740                 745                 750
Phe Arg Gln Pro Ile Ile Gly Ala Thr Ala Asn Ala Met Arg Glu Glu
        755                 760                 765
Arg Glu Arg Cys Met Ser Ala Gly Met Asn Asp Cys Leu Val Lys Pro
    770                 775                 780
Val Asp Leu Asn Ala Leu Gln Asn Cys Leu Ile Asn Ile Leu Lys Val
785                 790                 795                 800
Asp Arg
```

6R/2

Figure 6S

ORF1-8
SEQ ID NO:26

```
Met Leu Arg Arg Asn Asp Ala Gly Asn Tyr Met Leu Leu Asp Gln His
 1               5                  10                  15
Gly Gln Val Val Leu Ala Thr Asp Ala Glu Ala Leu Gly Ser Gly Ala
            20                  25                  30
Ser Arg Thr Leu Leu Arg Gly Asp Gly Phe Gly Phe Ile Gly Ala Gly
        35                  40                  45
Pro Leu Pro Gln His Met Val Leu Phe Gln His Val Gly Ser Ser Ser
    50                  55                  60
Trp Asp Leu Ile Tyr His Ile Gly Ile Gly Arg Leu Leu Leu Ala Leu
65                  70                  75                  80
Trp Leu Pro Leu Leu Leu Ala Ser Ala Leu Ala Leu Ala Val Gly Ile
                85                  90                  95
Leu Leu His Trp Leu Val Arg Ser Ile Glu Arg Arg Leu Ile Glu Pro
            100                 105                 110
Ala Lys Arg Arg Leu Glu Ala Leu Lys Glu Ser Glu Ala Phe Ser Arg
        115                 120                 125
Ala Val Ile Gln Ala Ala Pro Val Ala Leu Cys Val Leu Arg Arg Ala
    130                 135                 140
Asp Ala Ala Val Val Leu Glu Asn Pro Gln Ala Arg Gln Trp Leu Gly
145                 150                 155                 160
Asp Ser Glu Ala Ile Ala His Asp Ala Pro Arg Trp Ile Ser Gln Ala
                165                 170                 175
Phe Ala Gly Gly Val Lys Cys Ser Gly Glu Glu Leu Glu Thr Glu Ala
            180                 185                 190
Gly Leu His Leu His Leu Asn Tyr Thr Pro Thr Arg Tyr Asn Gly Glu
        195                 200                 205
Asp Val Leu Phe Cys Ala Phe Ser Glu Ile Ser Ala Arg Lys Arg Met
    210                 215                 220
Glu Ala Glu Leu Ala Arg Ala Lys Ser Leu Ala Asp Ala Ala Asn Glu
225                 230                 235                 240
Ala Lys Thr Leu Phe Leu Ala Thr Met Ser His Glu Ile Arg Thr Pro
                245                 250                 255
Leu Tyr Gly Met Leu Gly Thr Leu Glu Leu Leu Gly Arg Thr Glu Leu
            260                 265                 270
Ser Arg Gln Gln Ala Gly Tyr Leu Lys Ala Ile Gln His Ser Ser Ser
        275                 280                 285
Thr Leu Leu Gln Leu Ile Ser Asp Val Leu Asp Val Ser Lys Ile Glu
    290                 295                 300
Ala Gly Gln Leu Asp Leu Glu Cys Val Glu Phe Ser Pro Leu Glu Leu
305                 310                 315                 320
Thr Glu Glu Val Val Gln Ser Phe Thr Gly Ala Ala Gln Ala Lys Gly
                325                 330                 335
Leu Gln Leu Tyr Thr Cys Leu Ser Ala Glu Leu Pro Leu Arg Met Arg
            340                 345                 350
Gly Ala Ala Ala Ser Ile Arg Gln Ile Leu Asn Asn Leu Leu Ser Asn
        355                 360                 365
Ala Val Lys Phe Thr Asp Asn Gly Tyr Val Asn Val His Leu Lys Ala
    370                 375                 380
Ser Val Val Asp Ala Glu Cys Val Met Leu Thr Trp Gln Val Asn Asp
385                 390                 395                 400
Thr Gly Met Gly Ile Asn Val Glu Asp Gln Pro Arg Leu Phe Glu Pro
                405                 410                 415
Phe Tyr Gln Ile Arg Arg Ser Glu His Pro Val Ala Gly Thr Gly Leu
            420                 425                 430
Gly Leu Ser Ile Ser Gln Arg Leu Ala Gln Leu Met Asn Gly Ser Leu
        435                 440                 445
Lys Leu Val Ser Glu Leu Gly Leu Gly Ser Ser Phe Ser Leu Arg Leu
    450                 455                 460
```

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```
Pro Leu Glu Arg Ile Ala Met Gln Ala Glu Pro Gln Asp Leu Ala Gly
465                 470                 475                 480
Cys Ala Val Gln Val Leu Ala Pro Val Arg Asp Leu Thr Glu Cys Leu
                485                 490                 495
Cys Gly Trp Ile Ser Arg Trp Gly Gly Arg Ala Met Val Ala Thr Pro
            500                 505                 510
Arg Ser Leu Asp Glu Ala Asp Ala Thr Ser Leu Leu Val Glu Val Leu
        515                 520                 525
Leu Leu Glu Gly Ala Pro Met Phe Glu Ala Trp Pro Gly Cys Arg Val
    530                 535                 540
Glu Leu Ser Pro Gln Gly Asp Met Glu Pro Gln Ala Gln Gly Arg Asp
545                 550                 555                 560
Trp Leu Leu Gly Leu Asn Asn Leu Asp Gly Leu His Arg Ala Leu Gly
                565                 570                 575
Leu Ala His Gly Arg Leu Ala Asp Pro Ser Thr Pro Pro Ile Arg Leu
            580                 585                 590
Ala Pro Leu Arg Asn Leu Gly Leu Arg Val Leu Val Val Glu Asp Asn
        595                 600                 605
Ala Ile Asn Gln Leu Ile Leu Arg Asp Gln Met Glu Ala Leu Gly Cys
    610                 615                 620
Ser Val Glu Leu Leu Phe Asp Gly Arg Glu Ala Leu Leu His Cys Gln
625                 630                 635                 640
Thr Ala Cys Phe Asp Val Val Leu Thr Asp Ile Asn Met Pro Asn Met
                645                 650                 655
Asn Gly Tyr Glu Leu Thr Ala Glu Leu Arg Arg Gln Gly Phe Arg Gln
            660                 665                 670
Pro Ile Ile Gly Ala Thr Ala Asn Ala Met Arg Glu Glu Arg Glu Arg
        675                 680                 685
Cys Met Ser Ala Gly Met Asn Asp Cys Leu Val Lys Pro Val Asp Leu
    690                 695                 700
Asn Ala Leu Gln Asn Cys Leu Ile Asn Ile Leu Lys Val Asp Arg
705                 710                 715
```

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Figure 6T
ORF1-9
SEQ ID NO:27

```
Met Leu Leu Asp Gln His Gly Gln Val Val Leu Ala Thr Asp Ala Glu
 1               5                  10                  15
Ala Leu Gly Ser Gly Ala Ser Arg Thr Leu Leu Arg Gly Asp Gly Phe
            20                  25                  30
Gly Phe Ile Gly Ala Gly Pro Leu Pro Gln His Met Val Leu Phe Gln
        35                  40                  45
His Val Gly Ser Ser Ser Trp Asp Leu Ile Tyr His Ile Gly Ile Gly
    50                  55                  60
Arg Leu Leu Leu Ala Leu Trp Leu Pro Leu Leu Leu Ala Ser Ala Leu
65                  70                  75                  80
Ala Leu Ala Val Gly Ile Leu Leu His Trp Leu Val Arg Ser Ile Glu
                85                  90                  95
Arg Arg Leu Ile Glu Pro Ala Lys Arg Arg Leu Glu Ala Leu Lys Glu
            100                 105                 110
Ser Glu Ala Phe Ser Arg Ala Val Ile Gln Ala Ala Pro Val Ala Leu
        115                 120                 125
Cys Val Leu Arg Arg Ala Asp Ala Ala Val Val Leu Glu Asn Pro Gln
    130                 135                 140
Ala Arg Gln Trp Leu Gly Asp Ser Glu Ala Ile Ala His Asp Ala Pro
145                 150                 155                 160
Arg Trp Ile Ser Gln Ala Phe Ala Gly Gly Val Lys Cys Ser Gly Glu
                165                 170                 175
Glu Leu Glu Thr Glu Ala Gly Leu His Leu His Leu Asn Tyr Thr Pro
            180                 185                 190
Thr Arg Tyr Asn Gly Glu Asp Val Leu Phe Cys Ala Phe Ser Glu Ile
        195                 200                 205
Ser Ala Arg Lys Arg Met Glu Ala Glu Leu Ala Arg Ala Lys Ser Leu
    210                 215                 220
Ala Asp Ala Ala Asn Glu Ala Lys Thr Leu Phe Leu Ala Thr Met Ser
225                 230                 235                 240
His Glu Ile Arg Thr Pro Leu Tyr Gly Met Leu Gly Thr Leu Glu Leu
                245                 250                 255
Leu Gly Arg Thr Glu Leu Ser Arg Gln Gln Ala Gly Tyr Leu Lys Ala
            260                 265                 270
Ile Gln His Ser Ser Ser Thr Leu Leu Gln Leu Ile Ser Asp Val Leu
        275                 280                 285
Asp Val Ser Lys Ile Glu Ala Gly Gln Leu Asp Leu Glu Cys Val Glu
    290                 295                 300
Phe Ser Pro Leu Glu Leu Thr Glu Glu Val Val Gln Ser Phe Thr Gly
305                 310                 315                 320
Ala Ala Gln Ala Lys Gly Leu Gln Leu Tyr Thr Cys Leu Ser Ala Glu
                325                 330                 335
Leu Pro Leu Arg Met Arg Gly Ala Ala Ala Ser Ile Arg Gln Ile Leu
            340                 345                 350
Asn Asn Leu Leu Ser Asn Ala Val Lys Phe Thr Asp Asn Gly Tyr Val
        355                 360                 365
Asn Val His Leu Lys Ala Ser Val Val Asp Ala Glu Cys Val Met Leu
    370                 375                 380
Thr Trp Gln Val Asn Asp Thr Gly Met Gly Ile Asn Val Glu Asp Gln
385                 390                 395                 400
Pro Arg Leu Phe Glu Pro Phe Tyr Gln Ile Arg Arg Ser Glu His Pro
                405                 410                 415
Val Ala Gly Thr Gly Leu Gly Leu Ser Ile Ser Gln Arg Leu Ala Gln
            420                 425                 430
Leu Met Asn Gly Ser Leu Lys Leu Val Ser Glu Leu Gly Leu Gly Ser
        435                 440                 445
Ser Phe Ser Leu Arg Leu Pro Leu Glu Arg Ile Ala Met Gln Ala Glu
    450                 455                 460
```

6T/1

```
Pro Gln Asp Leu Ala Gly Cys Ala Val Gln Val Leu Ala Pro Val Arg
465                 470                 475                 480
Asp Leu Thr Glu Cys Leu Cys Gly Trp Ile Ser Arg Trp Gly Gly Arg
                485                 490                 495
Ala Met Val Ala Thr Pro Arg Ser Leu Asp Glu Ala Asp Ala Thr Ser
            500                 505                 510
Leu Leu Val Glu Val Leu Leu Leu Glu Gly Ala Pro Met Phe Glu Ala
        515                 520                 525
Trp Pro Gly Cys Arg Val Glu Leu Ser Pro Gln Gly Asp Met Glu Pro
    530                 535                 540
Gln Ala Gln Gly Arg Asp Trp Leu Leu Gly Leu Asn Asn Leu Asp Gly
545                 550                 555                 560
Leu His Arg Ala Leu Gly Leu Ala His Gly Arg Leu Ala Asp Pro Ser
                565                 570                 575
Thr Pro Pro Ile Arg Leu Ala Pro Leu Arg Asn Leu Gly Leu Arg Val
            580                 585                 590
Leu Val Val Glu Asp Asn Ala Ile Asn Gln Leu Ile Leu Arg Asp Gln
        595                 600                 605
Met Glu Ala Leu Gly Cys Ser Val Glu Leu Leu Phe Asp Gly Arg Glu
    610                 615                 620
Ala Leu Leu His Cys Gln Thr Ala Cys Phe Asp Val Val Leu Thr Asp
625                 630                 635                 640
Ile Asn Met Pro Asn Met Asn Gly Tyr Glu Leu Thr Ala Glu Leu Arg
                645                 650                 655
Arg Gln Gly Phe Arg Gln Pro Ile Ile Gly Ala Thr Ala Asn Ala Met
            660                 665                 670
Arg Glu Glu Arg Glu Arg Cys Met Ser Ala Gly Met Asn Asp Cys Leu
        675                 680                 685
Val Lys Pro Val Asp Leu Asn Ala Leu Gln Asn Cys Leu Ile Asn Ile
    690                 695                 700
Leu Lys Val Asp Arg
705
```

6T/2

Figure 6U

ORF1-10
SEQ ID NO:28

```
Met Val Leu Phe Gln His Val Gly Ser Ser Ser Trp Asp Leu Ile Tyr
 1               5                  10                  15
His Ile Gly Ile Gly Arg Leu Leu Leu Ala Leu Trp Leu Pro Leu Leu
            20                  25                  30
Leu Ala Ser Ala Leu Ala Leu Ala Val Gly Ile Leu Leu His Trp Leu
        35                  40                  45
Val Arg Ser Ile Glu Arg Arg Leu Ile Glu Pro Ala Lys Arg Arg Leu
    50                  55                  60
Glu Ala Leu Lys Glu Ser Glu Ala Phe Ser Arg Ala Val Ile Gln Ala
65                  70                  75                  80
Ala Pro Val Ala Leu Cys Val Leu Arg Arg Ala Asp Ala Ala Val Val
                85                  90                  95
Leu Glu Asn Pro Gln Ala Arg Gln Trp Leu Gly Asp Ser Glu Ala Ile
            100                 105                 110
Ala His Asp Ala Pro Arg Trp Ile Ser Gln Ala Phe Ala Gly Gly Val
        115                 120                 125
Lys Cys Ser Gly Glu Glu Leu Glu Thr Glu Ala Gly Leu His Leu His
    130                 135                 140
Leu Asn Tyr Thr Pro Thr Arg Tyr Asn Gly Glu Asp Val Leu Phe Cys
145                 150                 155                 160
Ala Phe Ser Glu Ile Ser Ala Arg Lys Arg Met Glu Ala Glu Leu Ala
                165                 170                 175
Arg Ala Lys Ser Leu Ala Asp Ala Ala Asn Glu Ala Lys Thr Leu Phe
            180                 185                 190
Leu Ala Thr Met Ser His Glu Ile Arg Thr Pro Leu Tyr Gly Met Leu
        195                 200                 205
Gly Thr Leu Glu Leu Leu Gly Arg Thr Glu Leu Ser Arg Gln Gln Ala
    210                 215                 220
Gly Tyr Leu Lys Ala Ile Gln His Ser Ser Ser Thr Leu Leu Gln Leu
225                 230                 235                 240
Ile Ser Asp Val Leu Asp Val Ser Lys Ile Glu Ala Gly Gln Leu Asp
                245                 250                 255
Leu Glu Cys Val Glu Phe Ser Pro Leu Glu Leu Thr Glu Glu Val Val
            260                 265                 270
Gln Ser Phe Thr Gly Ala Ala Gln Ala Lys Gly Leu Gln Leu Tyr Thr
        275                 280                 285
Cys Leu Ser Ala Glu Leu Pro Leu Arg Met Arg Gly Ala Ala Ala Ser
    290                 295                 300
Ile Arg Gln Ile Leu Asn Asn Leu Leu Ser Asn Ala Val Lys Phe Thr
305                 310                 315                 320
Asp Asn Gly Tyr Val Asn Val His Leu Lys Ala Ser Val Val Asp Ala
                325                 330                 335
Glu Cys Val Met Leu Thr Trp Gln Val Asn Asp Thr Gly Met Gly Ile
            340                 345                 350
Asn Val Glu Asp Gln Pro Arg Leu Phe Glu Pro Phe Tyr Gln Ile Arg
        355                 360                 365
Arg Ser Glu His Pro Val Ala Gly Thr Gly Leu Gly Leu Ser Ile Ser
    370                 375                 380
Gln Arg Leu Ala Gln Leu Met Asn Gly Ser Leu Lys Leu Val Ser Glu
385                 390                 395                 400
Leu Gly Leu Gly Ser Ser Phe Ser Leu Arg Leu Pro Leu Glu Arg Ile
                405                 410                 415
Ala Met Gln Ala Glu Pro Gln Asp Leu Ala Gly Cys Ala Val Gln Val
            420                 425                 430
Leu Ala Pro Val Arg Asp Leu Thr Glu Cys Leu Cys Gly Trp Ile Ser
        435                 440                 445
Arg Trp Gly Gly Arg Ala Met Val Ala Thr Pro Arg Ser Leu Asp Glu
    450                 455                 460
```

6U/1

```
Ala Asp Ala Thr Ser Leu Leu Val Glu Val Leu Leu Leu Glu Gly Ala
465                 470                 475                 480
Pro Met Phe Glu Ala Trp Pro Gly Cys Arg Val Glu Leu Ser Pro Gln
                485                 490                 495
Gly Asp Met Glu Pro Gln Ala Gln Gly Arg Asp Trp Leu Leu Gly Leu
            500                 505                 510
Asn Asn Leu Asp Gly Leu His Arg Ala Leu Gly Leu Ala His Gly Arg
        515                 520                 525
Leu Ala Asp Pro Ser Thr Pro Pro Ile Arg Leu Ala Pro Leu Arg Asn
    530                 535                 540
Leu Gly Leu Arg Val Leu Val Val Glu Asp Asn Ala Ile Asn Gln Leu
545                 550                 555                 560
Ile Leu Arg Asp Gln Met Glu Ala Leu Gly Cys Ser Val Glu Leu Leu
                565                 570                 575
Phe Asp Gly Arg Glu Ala Leu Leu His Cys Gln Thr Ala Cys Phe Asp
            580                 585                 590
Val Val Leu Thr Asp Ile Asn Met Pro Asn Met Asn Gly Tyr Glu Leu
        595                 600                 605
Thr Ala Glu Leu Arg Arg Gln Gly Phe Arg Gln Pro Ile Ile Gly Ala
    610                 615                 620
Thr Ala Asn Ala Met Arg Glu Glu Arg Glu Arg Cys Met Ser Ala Gly
625                 630                 635                 640
Met Asn Asp Cys Leu Val Lys Pro Val Asp Leu Asn Ala Leu Gln Asn
                645                 650                 655
Cys Leu Ile Asn Ile Leu Lys Val Asp Arg
            660                 665
```

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Figure 6V

ORF1-11
SEQ ID NO:29

```
Met Glu Ala Glu Leu Ala Arg Ala Lys Ser Leu Ala Asp Ala Ala Asn
 1               5                  10                  15
Glu Ala Lys Thr Leu Phe Leu Ala Thr Met Ser His Glu Ile Arg Thr
            20                  25                  30
Pro Leu Tyr Gly Met Leu Gly Thr Leu Glu Leu Leu Gly Arg Thr Glu
        35                  40                  45
Leu Ser Arg Gln Gln Ala Gly Tyr Leu Lys Ala Ile Gln His Ser Ser
    50                  55                  60
Ser Thr Leu Leu Gln Leu Ile Ser Asp Val Leu Asp Val Ser Lys Ile
65                  70                  75                  80
Glu Ala Gly Gln Leu Asp Leu Glu Cys Val Glu Phe Ser Pro Leu Glu
                85                  90                  95
Leu Thr Glu Glu Val Val Gln Ser Phe Thr Gly Ala Ala Gln Ala Lys
            100                 105                 110
Gly Leu Gln Leu Tyr Thr Cys Leu Ser Ala Glu Leu Pro Leu Arg Met
        115                 120                 125
Arg Gly Ala Ala Ala Ser Ile Arg Gln Ile Leu Asn Asn Leu Leu Ser
    130                 135                 140
Asn Ala Val Lys Phe Thr Asp Asn Gly Tyr Val Asn Val His Leu Lys
145                 150                 155                 160
Ala Ser Val Val Asp Ala Glu Cys Val Met Leu Thr Trp Gln Val Asn
                165                 170                 175
Asp Thr Gly Met Gly Ile Asn Val Glu Asp Gln Pro Arg Leu Phe Glu
            180                 185                 190
Pro Phe Tyr Gln Ile Arg Arg Ser Glu His Pro Val Ala Gly Thr Gly
        195                 200                 205
Leu Gly Leu Ser Ile Ser Gln Arg Leu Ala Gln Leu Met Asn Gly Ser
    210                 215                 220
Leu Lys Leu Val Ser Glu Leu Gly Leu Gly Ser Ser Phe Ser Leu Arg
225                 230                 235                 240
Leu Pro Leu Glu Arg Ile Ala Met Gln Ala Glu Pro Gln Asp Leu Ala
                245                 250                 255
Gly Cys Ala Val Gln Val Leu Ala Pro Val Arg Asp Leu Thr Glu Cys
            260                 265                 270
Leu Cys Gly Trp Ile Ser Arg Trp Gly Gly Arg Ala Met Val Ala Thr
        275                 280                 285
Pro Arg Ser Leu Asp Glu Ala Asp Ala Thr Ser Leu Leu Val Glu Val
    290                 295                 300
Leu Leu Leu Glu Gly Ala Pro Met Phe Glu Ala Trp Pro Gly Cys Arg
305                 310                 315                 320
Val Glu Leu Ser Pro Gln Gly Asp Met Glu Pro Gln Ala Gln Gly Arg
                325                 330                 335
Asp Trp Leu Leu Gly Leu Asn Asn Leu Asp Gly Leu His Arg Ala Leu
            340                 345                 350
Gly Leu Ala His Gly Arg Leu Ala Asp Pro Ser Thr Pro Pro Ile Arg
        355                 360                 365
Leu Ala Pro Leu Arg Asn Leu Gly Leu Arg Val Leu Val Val Glu Asp
    370                 375                 380
Asn Ala Ile Asn Gln Leu Ile Leu Arg Asp Gln Met Glu Ala Leu Gly
385                 390                 395                 400
Cys Ser Val Glu Leu Leu Phe Asp Gly Arg Glu Ala Leu Leu His Cys
                405                 410                 415
Gln Thr Ala Cys Phe Asp Val Val Leu Thr Asp Ile Asn Met Pro Asn
            420                 425                 430
Met Asn Gly Tyr Glu Leu Thr Ala Glu Leu Arg Arg Gln Gly Phe Arg
        435                 440                 445
Gln Pro Ile Ile Gly Ala Thr Ala Asn Ala Met Arg Glu Glu Arg Glu
    450                 455                 460
```

6V/1

```
Arg Cys Met Ser Ala Gly Met Asn Asp Cys Leu Val Lys Pro Val Asp
465                 470                 475                 480
Leu Asn Ala Leu Gln Asn Cys Leu Ile Asn Ile Leu Lys Val Asp Arg
                485                 490                 495
```

6V/2

Figure 7a

ORF3-2
SEQ ID NO:30

```
atggatgtta tacgggagca tgaggtattt cttgggcgca tcgctcgaaa aagcgacaag 60
accacccaga agtacgacta tgacgtggtg cctttgcagc ggcacttgtt ggcaaaggaa 120
aacggattag cggtctatga gggacgggag ttttcctttg ctatgccatt tctactggct 180
accaagcacg cgttgagcgc cgattcctcg ggagatccgt tttcgctcgg tgtattgctc 240
gccaatttct acggaagctt ctggagtgtt tccgcctatc ccgcgccaca gttactgatc 300
tttgatcttt ccggcagcac ccgcctggca gtgccgtcga ttccctccac agcgcagcgt 360
gacaggttga gcggaagcta tccgatgata gtcgagcgca ttctggcgcg cttgcgcacc 420
cggccggtgg gggaggacgc tcagcgtgtc cattggatac gcgctgatcg ctatcgcgac 480
tcggcgctgg agatgttggg agtcgcccgg gttgatctgc cggaaacact ctggtggcac 540
gacgagccga accatctgat catcgctgcg agcctgcttg atctcaggcg aatcaatgac 600
ttcgaacagt tggttgagcg cccggcattc gattcgtaca gcctggtatc gccggatggc 660
gaggtattgc tcggcgcggc ccctgcgacc ggcctgaggg atggcctgaa cctcacccga 720
caggggtcg ccgttcaact gcgcagccag cctgagaacg gctggctcgc ggtctaccga 780
accgactacg gcaatttctt tcgccactcc cggtggctgg tggcaggtct gctgctgacc 840
ccggcgctgc tcctggccgg ttggctcggg atgcgttggt acaccagcag cgtcgtcaac 900
ccggtgcatc gggcgcaccg gcaactggtg gagagcgaca ccttcagccg gacgctgata 960
cagaccgcgc cggtggctct ggtggtgctg acccaggatg accagcaact ggtgacctgc 1020
aaccacttgg ccgcccagtg gctgggcggg cccacggaga tccttgggct gacttccaac 1080
tggaagcttt tcgatgcgcg tgggcaggta ccaggagaca tctgtatcca ggtcggtggg 1140
cgctatttgc agaccgcctt cgcggcgacc cgctatgccg gcaccgaggc ggtactgtgc 1200
gtattcaacg acatcacggt ccactgcgag gcggagaccg cgctgtccaa tgcgaagcga 1260
gcagcggatg ccgccagcca ggccaagacc ctgttcctgg cccgcatgag ccatgaaatc 1320
cgtactcccc tgtacggtgt ccttggcacc ctggagttgc tcgacctgac caccctgaac 1380
gagcggcaac gcgcctacct acgcaccatc cagagttcgt ctgcgacgct catgcaactg 1440
attagcgatg tgctggatgt ctcgaagatc gaagcggggc agatggctct gaccctggcc 1500
gccttcaatc cgctggacct agtgcgggaa gtgcttggca actttgccgc cagcgccatg 1560
gccaaggacc tgcaggtaga cccgctcgat actcttgcgc ttgaggcgca ggtcgcgcat 1620
ggcttcgaag aaagcgttct gttcgaggtt gctggtggct cggtcggcca tttcgaagag 1680
ggtgtcgtcg gcgttgtcga acaacgcctg caacgcctgt ttcagctgca gcgccgcctt 1740
gtcgcgcacc tgcacgagga tgaccggcag gcgccccgct ccggcgttcg gcgacggctc 1800
ggaagcgacc ctggtcaggt gcaccacatt ggcatcgttc tgcatcggga ctctcctgcc 1860
accctcgcgg ccgcgcatgg aatggcaaaa atcgggcaca gaggatcgat tggcgtcgtc 1920
cgtaacgtca atttccaggc gtcaaaaaca agtatctaca ttcattatag agatactttc 1980
aaatctagat ag                                                      1992
```

Figure 7B

ORF3-3
SEQ ID NO:31

```
atgccatttc tactggctac caagcacgcg ttgagcgccg attcctcggg agatccgttt 60
tcgctcggtg tattgctcgc caatttctac ggaagcttct ggagtgtttc cgcctatccc 120
gcgccacagt tactgatctt tgatctttcc ggcagcaccc gcctggcagt gccgtcgatt 180
ccctccacag cgcagcgtga caggttgagc ggaagctatc cgatgatagt cgagcgcatt 240
ctggcgcgct tgcgcacccg gccggtgggg gaggacgctc agcgtgtcca ttggatacgc 300
gctgatcgct atcgcgactc ggcgctggag atgttgggag tcgcccgggt tgatctgccg 360
gaaacactct ggtggcacga cgagccgaac catctgatca tcgctgcgag cctgcttgat 420
ctcaggcgaa tcaatgactt cgaacagttg gttgagcgcc cggcattcga ttcgtacagc 480
ctggtatcgc cggatggcga ggtattgctc ggcgcggccc ctgcgaccgg cctgagggat 540
ggcctgaacc tcacccgaca gggggtcgcc gttcaactgc gcagccagcc tgagaacggc 600
tggctcgcgg tctaccgaac cgactacggc aatttctttc gccactcccg gtggctggtg 660
gcaggtctgc tgctgacccc ggcgctgctc ctggccggtt ggctcgggat gcgttggtac 720
accagcagcg tcgtcaaccc ggtgcatcgg gcgcaccggc aactggtgga gagcgacacc 780
ttcagccgga cgctgataca gaccgcgccg gtggctctgg tggtgctgac ccaggatgac 840
cagcaactgg tgacctgcaa ccacttggcc gcccagtggc tgggcgggcc cacggagatc 900
cttgggctga cttccaactg gaagcttttc gatgcgcgtg ggcaggtacc aggagacatc 960
tgtatccagg tcggtgggcg ctatttgcag accgccttcg cggcgacccg ctatgccggc 1020
accgaggcgg tactgtgcgt attcaacgac atcacggtcc actgcgaggc ggagaccgcg 1080
ctgtccaatg cgaagcgagc agcggatgcc gccagccagg ccaagaccct gttcctggcc 1140
cgcatgagcc atgaaatccg tactcccctg tacggtgtcc ttggcaccct ggagttgctc 1200
gacctgacca ccctgaacga gcggcaacgc gcctacctac gcaccatcca gagttcgtct 1260
gcgacgctca tgcaactgat tagcgatgtg ctggatgtct cgaagatcga agcggggcag 1320
atggctctga ccctggccgc cttcaatccg ctggacctag tgcgggaagt gcttggcaac 1380
tttgccgcca gcgccatggc caaggacctg caggtagacc cgctcgatac tcttgcgctt 1440
gaggcgcagg tcgcgcatgg cttcgaagaa agcgttctgt tcgaggttgc tggtggctcg 1500
gtcggccatt tcgaagaggg tgtcgtcggc gttgtcgaac aacgcctgca acgcctgttt 1560
cagctgcagc gccgccttgt cgcgcacctg cacgaggatg accggcaggc gccccgctcc 1620
ggcgttcggc gacggctcgg aagcgaccct ggtcaggtgc accacattgg catcgttctg 1680
catcgggact ctcctgccac cctcgcggcc gcgcatggaa tggcaaaaat cgggcacaga 1740
ggatcgattg gcgtcgtccg taacgtcaat ttccaggcgt caaaaacaag tatctacatt 1800
cattatagag atactttcaa atctagatag                                  1830
```

Figure 7C

ORF3-4
SEQ ID NO:32

```
atgatagtcg agcgcattct ggcgcgcttg cgcacccggc cggtggggga ggacgctcag 60
cgtgtccatt ggatacgcgc tgatcgctat cgcgactcgg cgctggagat gttgggagtc 120
gcccgggttg atctgccgga aacactctgg tggcacgacg agccgaacca tctgatcatc 180
gctgcgagcc tgcttgatct caggcgaatc aatgacttcg aacagttggt tgagcgcccg 240
gcattcgatt cgtacagcct ggtatcgccg gatggcgagg tattgctcgg cgcggcccct 300
gcgaccggcc tgagggatgg cctgaacctc acccgacagg gggtcgccgt tcaactgcgc 360
agccagcctg agaacggctg gctcgcggtc taccgaaccg actacggcaa tttctttcgc 420
cactcccggt ggctggtggc aggtctgctg ctgaccccgg cgctgctcct ggccggttgg 480
ctcgggatgc gttggtacac cagcagcgtc gtcaacccgg tgcatcgggc gcaccggcaa 540
ctggtggaga gcgacacctt cagccggacg ctgatacaga ccgcgccggt ggctctggtg 600
gtgctgaccc aggatgacca gcaactggtg acctgcaacc acttggccgc ccagtggctg 660
ggcgggccca cggagatcct tgggctgact tccaactgga agcttttcga tgcgcgtggg 720
caggtaccag gagacatctg tatccaggtc ggtgggcgct atttgcagac cgccttcgcg 780
gcgacccgct atgccggcac cgaggcggta ctgtgcgtat tcaacgacat cacggtccac 840
tgcgaggcgg agaccgcgct gtccaatgcg aagcgagcag cggatgccgc cagccaggcc 900
aagaccctgt tcctggcccg catgagccat gaaatccgta ctcccctgta cggtgtcctt 960
ggcaccctgg agttgctcga cctgaccacc ctgaacgagc ggcaacgcgc ctacctacgc 1020
accatccaga gttcgtctgc gacgctcatg caactgatta gcgatgtgct ggatgtctcg 1080
aagatcgaag cggggcagat ggctctgacc ctggccgcct tcaatccgct ggacctagtg 1140
cgggaagtgc ttggcaactt tgccgccagc gccatggcca aggacctgca ggtagacccg 1200
ctcgatactc ttgcgcttga ggcgcaggtc gcgcatggct tcgaagaaag cgttctgttc 1260
gaggttgctg gtggctcggt cggccatttc gaagagggtg tcgtcggcgt tgtcgaacaa 1320
cgcctgcaac gcctgtttca gctgcagcgc cgccttgtcg cgcacctgca cgaggatgac 1380
cggcaggcgc cccgctccgg cgttcggcga cggctcggaa gcgaccctgg tcaggtgcac 1440
cacattggca tcgttctgca tcgggactct cctgccaccc tcgcggccgc gcatggaatg 1500
gcaaaaatcg ggcacagagg atcgattggc gtcgtccgta acgtcaattt ccaggcgtca 1560
aaaacaagta tctacattca ttatagagat actttcaaat ctagatag 1608
```

Figure 7D
ORF3-5
SEQ ID NO:33

```
atgttgggag tcgcccgggt tgatctgccg gaaacactct ggtggcacga cgagccgaac 60
catctgatca tcgctgcgag cctgcttgat ctcaggcgaa tcaatgactt cgaacagttg 120
gttgagcgcc cggcattcga ttcgtacagc ctggtatcgc cggatggcga ggtattgctc 180
ggcgcggccc ctgcgaccgg cctgagggat ggcctgaacc tcacccgaca gggggtcgcc 240
gttcaactgc gcagccagcc tgagaacggc tggctcgcgg tctaccgaac cgactacggc 300
aatttctttc gccactcccg gtggctggtg gcaggtctgc tgctgacccc ggcgctgctc 360
ctggccggtt ggctcgggat gcgttggtac accagcagcg tcgtcaaccc ggtgcatcgg 420
gcgcaccggc aactggtgga gagcgacacc ttcagccgga cgctgataca gaccgcgccg 480
gtggctctgg tggtgctgac ccaggatgac cagcaactgg tgacctgcaa ccacttggcc 540
gcccagtggc tgggcgggcc cacggagatc cttgggctga cttccaactg gaagcttttc 600
gatgcgcgtg ggcaggtacc aggagacatc tgtatccagg tcggtgggcg ctatttgcag 660
accgccttcg cggcgacccg ctatgccggc accgaggcgg tactgtgcgt attcaacgac 720
atcacggtcc actgcgaggc ggagaccgcg ctgtccaatg cgaagcgagc agcggatgcc 780
gccagccagg ccaagaccct gttcctggcc cgcatgagcc atgaaatccg tactcccctg 840
tacggtgtcc ttggcaccct ggagttgctc gacctgacca ccctgaacga gcggcaacgc 900
gcctacctac gcaccatcca gagttcgtct gcgacgctca tgcaactgat tagcgatgtg 960
ctggatgtct cgaagatcga agcggggcag atggctctga ccctggccgc cttcaatccg 1020
ctggacctag tgcgggaagt gcttggcaac tttgccgcca gcgccatggc caaggacctg 1080
caggtagacc cgctcgatac tcttgcgctt gaggcgcagg tcgcgcatgg cttcgaagaa 1140
agcgttctgt tcgaggttgc tggtggctcg gtcggccatt tcgaagaggg tgtcgtcggc 1200
gttgtcgaac aacgcctgca acgcctgttt cagctgcagc gccgccttgt cgcgcacctg 1260
cacgaggatg accggcaggc gccccgctcc ggcgttcggc gacggctcgg aagcgaccct 1320
ggtcaggtgc accacattgg catcgttctg catcgggact ctcctgccac cctcgcggcc 1380
gcgcatggaa tggcaaaaat cgggcacaga ggatcgattg gcgtcgtccg taacgtcaat 1440
ttccaggcgt caaaaacaag tatctacatt cattatagag atactttcaa atctagatag 1500
```

Figure 7E

ORF3-6
SEQ ID NO:34

```
atgcgttggt acaccagcag cgtcgtcaac ccggtgcatc gggcgcaccg gcaactggtg  60
gagagcgaca ccttcagccg gacgctgata cagaccgcgc cggtggctct ggtggtgctg 120
acccaggatg accagcaact ggtgacctgc aaccacttgg ccgcccagtg gctgggcggg 180
cccacggaga tccttgggct gacttccaac tggaagcttt tcgatgcgcg tgggcaggta 240
ccaggagaca tctgtatcca ggtcggtggg cgctatttgc agaccgcctt cgcggcgacc 300
cgctatgccg gcaccgaggc ggtactgtgc gtattcaacg acatcacggt ccactgcgag 360
gcggagaccg cgctgtccaa tgcgaagcga gcagcggatg ccgccagcca ggccaagacc 420
ctgttcctgg cccgcatgag ccatgaaatc cgtactcccc tgtacggtgt ccttggcacc 480
ctggagttgc tcgacctgac caccctgaac gagcggcaac gcgcctacct acgcaccatc 540
cagagttcgt ctgcgacgct catgcaactg attagcgatg tgctggatgt ctcgaagatc 600
gaagcggggc agatggctct gaccctggcc gccttcaatc cgctggacct agtgcgggaa 660
gtgcttggca actttgccgc cagcgccatg gccaaggacc tgcaggtaga cccgctcgat 720
actcttgcgc ttgaggcgca ggtcgcgcat ggcttcgaag aaagcgttct gttcgaggtt 780
gctggtggct cggtcggcca tttcgaagag ggtgtcgtcg gcgttgtcga acaacgcctg 840
caacgcctgt ttcagctgca gcgccgcctt gtcgcgcacc tgcacgagga tgaccggcag 900
gcgccccgct ccggcgttcg gcgacggctc ggaagcgacc ctggtcaggt gcaccacatt 960
ggcatcgttc tgcatcggga ctctcctgcc accctcgcgg ccgcgcatgg aatggcaaaa 1020
atcgggcaca gaggatcgat tggcgtcgtc cgtaacgtca atttccaggc gtcaaaaaca 1080
agtatctaca ttcattatag agatactttc aaatctagat ag                    1122
```

Figure 7F

ORF3-2
SEQ ID NO:35

```
Met Asp Val Ile Arg Glu His Glu Val Phe Leu Gly Arg Ile Ala Arg
 1               5                  10                  15
Lys Ser Asp Lys Thr Thr Gln Lys Tyr Asp Tyr Asp Val Val Pro Leu
            20                  25                  30
Gln Arg His Leu Leu Ala Lys Glu Asn Gly Leu Ala Val Tyr Glu Gly
        35                  40                  45
Arg Glu Phe Ser Phe Ala Met Pro Phe Leu Leu Ala Thr Lys His Ala
    50                  55                  60
Leu Ser Ala Asp Ser Ser Gly Asp Pro Phe Ser Leu Gly Val Leu Leu
65                  70                  75                  80
Ala Asn Phe Tyr Gly Ser Phe Trp Ser Val Ser Ala Tyr Pro Ala Pro
                85                  90                  95
Gln Leu Leu Ile Phe Asp Leu Ser Gly Ser Thr Arg Leu Ala Val Pro
            100                 105                 110
Ser Ile Pro Ser Thr Ala Gln Arg Asp Arg Leu Ser Gly Ser Tyr Pro
        115                 120                 125
Met Ile Val Glu Arg Ile Leu Ala Arg Leu Arg Thr Arg Pro Val Gly
    130                 135                 140
Glu Asp Ala Gln Arg Val His Trp Ile Arg Ala Asp Arg Tyr Arg Asp
145                 150                 155                 160
Ser Ala Leu Glu Met Leu Gly Val Ala Arg Val Asp Leu Pro Glu Thr
                165                 170                 175
Leu Trp Trp His Asp Glu Pro Asn His Leu Ile Ile Ala Ala Ser Leu
            180                 185                 190
Leu Asp Leu Arg Arg Ile Asn Asp Phe Glu Gln Leu Val Glu Arg Pro
        195                 200                 205
Ala Phe Asp Ser Tyr Ser Leu Val Ser Pro Asp Gly Glu Val Leu Leu
    210                 215                 220
Gly Ala Ala Pro Ala Thr Gly Leu Arg Asp Gly Leu Asn Leu Thr Arg
225                 230                 235                 240
Gln Gly Val Ala Val Gln Leu Arg Ser Gln Pro Glu Asn Gly Trp Leu
                245                 250                 255
Ala Val Tyr Arg Thr Asp Tyr Gly Asn Phe Phe Arg His Ser Arg Trp
            260                 265                 270
Leu Val Ala Gly Leu Leu Leu Thr Pro Ala Leu Leu Leu Ala Gly Trp
        275                 280                 285
Leu Gly Met Arg Trp Tyr Thr Ser Ser Val Val Asn Pro Val His Arg
    290                 295                 300
Ala His Arg Gln Leu Val Glu Ser Asp Thr Phe Ser Arg Thr Leu Ile
305                 310                 315                 320
Gln Thr Ala Pro Val Ala Leu Val Val Leu Thr Gln Asp Asp Gln Gln
                325                 330                 335
Leu Val Thr Cys Asn His Leu Ala Ala Gln Trp Leu Gly Gly Pro Thr
            340                 345                 350
Glu Ile Leu Gly Leu Thr Ser Asn Trp Lys Leu Phe Asp Ala Arg Gly
        355                 360                 365
Gln Val Pro Gly Asp Ile Cys Ile Gln Val Gly Gly Arg Tyr Leu Gln
    370                 375                 380
Thr Ala Phe Ala Ala Thr Arg Tyr Ala Gly Thr Glu Ala Val Leu Cys
385                 390                 395                 400
Val Phe Asn Asp Ile Thr Val His Cys Glu Ala Glu Thr Ala Leu Ser
                405                 410                 415
Asn Ala Lys Arg Ala Ala Asp Ala Ala Ser Gln Ala Lys Thr Leu Phe
            420                 425                 430
Leu Ala Arg Met Ser His Glu Ile Arg Thr Pro Leu Tyr Gly Val Leu
        435                 440                 445
Gly Thr Leu Glu Leu Leu Asp Leu Thr Thr Leu Asn Glu Arg Gln Arg
    450                 455                 460
```

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```
Ala Tyr Leu Arg Thr Ile Gln Ser Ser Ser Ala Thr Leu Met Gln Leu
465                 470                 475                 480
Ile Ser Asp Val Leu Asp Val Ser Lys Ile Glu Ala Gly Gln Met Ala
                485                 490                 495
Leu Thr Leu Ala Ala Phe Asn Pro Leu Asp Leu Val Arg Glu Val Leu
            500                 505                 510
Gly Asn Phe Ala Ala Ser Ala Met Ala Lys Asp Leu Gln Val Asp Pro
        515                 520                 525
Leu Asp Thr Leu Ala Leu Glu Ala Gln Val Ala His Gly Phe Glu Glu
    530                 535                 540
Ser Val Leu Phe Glu Val Ala Gly Gly Ser Val Gly His Phe Glu Glu
545                 550                 555                 560
Gly Val Val Gly Val Val Glu Gln Arg Leu Gln Arg Leu Phe Gln Leu
                565                 570                 575
Gln Arg Arg Leu Val Ala His Leu His Glu Asp Asp Arg Gln Ala Pro
            580                 585                 590
Arg Ser Gly Val Arg Arg Arg Leu Gly Ser Asp Pro Gly Gln Val His
        595                 600                 605
His Ile Gly Ile Val Leu His Arg Asp Ser Pro Ala Thr Leu Ala Ala
    610                 615                 620
Ala His Gly Met Ala Lys Ile Gly His Arg Gly Ser Ile Gly Val Val
625                 630                 635                 640
Arg Asn Val Asn Phe Gln Ala Ser Lys Thr Ser Ile Tyr Ile His Tyr
                645                 650                 655
Arg Asp Thr Phe Lys Ser Arg
            660
```

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Figure 7G

ORF 3-3
SEQ ID NO:36

```
Met Pro Phe Leu Leu Ala Thr Lys His Ala Leu Ser Ala Asp Ser Ser
 1               5                  10                  15
Gly Asp Pro Phe Ser Leu Gly Val Leu Leu Ala Asn Phe Tyr Gly Ser
            20                  25                  30
Phe Trp Ser Val Ser Ala Tyr Pro Ala Pro Gln Leu Leu Ile Phe Asp
        35                  40                  45
Leu Ser Gly Ser Thr Arg Leu Ala Val Pro Ser Ile Pro Ser Thr Ala
    50                  55                  60
Gln Arg Asp Arg Leu Ser Gly Ser Tyr Pro Met Ile Val Glu Arg Ile
65                  70                  75                  80
Leu Ala Arg Leu Arg Thr Arg Pro Val Gly Glu Asp Ala Gln Arg Val
                85                  90                  95
His Trp Ile Arg Ala Asp Arg Tyr Arg Asp Ser Ala Leu Glu Met Leu
            100                 105                 110
Gly Val Ala Arg Val Asp Leu Pro Glu Thr Leu Trp Trp His Asp Glu
        115                 120                 125
Pro Asn His Leu Ile Ile Ala Ala Ser Leu Leu Asp Leu Arg Arg Ile
    130                 135                 140
Asn Asp Phe Glu Gln Leu Val Glu Arg Pro Ala Phe Asp Ser Tyr Ser
145                 150                 155                 160
Leu Val Ser Pro Asp Gly Glu Val Leu Leu Gly Ala Ala Pro Ala Thr
                165                 170                 175
Gly Leu Arg Asp Gly Leu Asn Leu Thr Arg Gln Gly Val Ala Val Gln
            180                 185                 190
Leu Arg Ser Gln Pro Glu Asn Gly Trp Leu Ala Val Tyr Arg Thr Asp
        195                 200                 205
Tyr Gly Asn Phe Phe Arg His Ser Arg Trp Leu Val Ala Gly Leu Leu
    210                 215                 220
Leu Thr Pro Ala Leu Leu Leu Ala Gly Trp Leu Gly Met Arg Trp Tyr
225                 230                 235                 240
Thr Ser Ser Val Val Asn Pro Val His Arg Ala His Arg Gln Leu Val
                245                 250                 255
Glu Ser Asp Thr Phe Ser Arg Thr Leu Ile Gln Thr Ala Pro Val Ala
            260                 265                 270
Leu Val Val Leu Thr Gln Asp Asp Gln Gln Leu Val Thr Cys Asn His
        275                 280                 285
Leu Ala Ala Gln Trp Leu Gly Gly Pro Thr Glu Ile Leu Gly Leu Thr
    290                 295                 300
Ser Asn Trp Lys Leu Phe Asp Ala Arg Gly Gln Val Pro Gly Asp Ile
305                 310                 315                 320
Cys Ile Gln Val Gly Gly Arg Tyr Leu Gln Thr Ala Phe Ala Ala Thr
                325                 330                 335
Arg Tyr Ala Gly Thr Glu Ala Val Leu Cys Val Phe Asn Asp Ile Thr
            340                 345                 350
Val His Cys Glu Ala Glu Thr Ala Leu Ser Asn Ala Lys Arg Ala Ala
        355                 360                 365
Asp Ala Ala Ser Gln Ala Lys Thr Leu Phe Leu Ala Arg Met Ser His
    370                 375                 380
Glu Ile Arg Thr Pro Leu Tyr Gly Val Leu Gly Thr Leu Glu Leu Leu
385                 390                 395                 400
Asp Leu Thr Thr Leu Asn Glu Arg Gln Arg Ala Tyr Leu Arg Thr Ile
                405                 410                 415
Gln Ser Ser Ser Ala Thr Leu Met Gln Leu Ile Ser Asp Val Leu Asp
            420                 425                 430
Val Ser Lys Ile Glu Ala Gly Gln Met Ala Leu Thr Leu Ala Ala Phe
        435                 440                 445
Asn Pro Leu Asp Leu Val Arg Glu Val Leu Gly Asn Phe Ala Ala Ser
    450                 455                 460
```

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```
Ala Met Ala Lys Asp Leu Gln Val Asp Pro Leu Asp Thr Leu Ala Leu
465                 470                 475                 480
Glu Ala Gln Val Ala His Gly Phe Glu Glu Ser Val Leu Phe Glu Val
                485                 490                 495
Ala Gly Gly Ser Val Gly His Phe Glu Glu Gly Val Val Gly Val Val
            500                 505                 510
Glu Gln Arg Leu Gln Arg Leu Phe Gln Leu Gln Arg Arg Leu Val Ala
        515                 520                 525
His Leu His Glu Asp Asp Arg Gln Ala Pro Arg Ser Gly Val Arg Arg
    530                 535                 540
Arg Leu Gly Ser Asp Pro Gly Gln Val His His Ile Gly Ile Val Leu
545                 550                 555                 560
His Arg Asp Ser Pro Ala Thr Leu Ala Ala Ala His Gly Met Ala Lys
                565                 570                 575
Ile Gly His Arg Gly Ser Ile Gly Val Val Arg Asn Val Asn Phe Gln
            580                 585                 590
Ala Ser Lys Thr Ser Ile Tyr Ile His Tyr Arg Asp Thr Phe Lys Ser
        595                 600                 605
Arg
```

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Figure 7H

ORF3-4
SEQ ID NO:37

```
Met Ile Val Glu Arg Ile Leu Ala Arg Leu Arg Thr Arg Pro Val Gly
 1               5                  10                  15
Glu Asp Ala Gln Arg Val His Trp Ile Arg Ala Asp Arg Tyr Arg Asp
            20                  25                  30
Ser Ala Leu Glu Met Leu Gly Val Ala Arg Val Asp Leu Pro Glu Thr
        35                  40                  45
Leu Trp Trp His Asp Glu Pro Asn His Leu Ile Ile Ala Ala Ser Leu
    50                  55                  60
Leu Asp Leu Arg Arg Ile Asn Asp Phe Glu Gln Leu Val Glu Arg Pro
65                  70                  75                  80
Ala Phe Asp Ser Tyr Ser Leu Val Ser Pro Asp Gly Glu Val Leu Leu
                85                  90                  95
Gly Ala Ala Pro Ala Thr Gly Leu Arg Asp Gly Leu Asn Leu Thr Arg
            100                 105                 110
Gln Gly Val Ala Val Gln Leu Arg Ser Gln Pro Glu Asn Gly Trp Leu
        115                 120                 125
Ala Val Tyr Arg Thr Asp Tyr Gly Asn Phe Phe Arg His Ser Arg Trp
    130                 135                 140
Leu Val Ala Gly Leu Leu Leu Thr Pro Ala Leu Leu Leu Ala Gly Trp
145                 150                 155                 160
Leu Gly Met Arg Trp Tyr Thr Ser Ser Val Val Asn Pro Val His Arg
                165                 170                 175
Ala His Arg Gln Leu Val Glu Ser Asp Thr Phe Ser Arg Thr Leu Ile
            180                 185                 190
Gln Thr Ala Pro Val Ala Leu Val Val Leu Thr Gln Asp Asp Gln Gln
        195                 200                 205
Leu Val Thr Cys Asn His Leu Ala Ala Gln Trp Leu Gly Gly Pro Thr
    210                 215                 220
Glu Ile Leu Gly Leu Thr Ser Asn Trp Lys Leu Phe Asp Ala Arg Gly
225                 230                 235                 240
Gln Val Pro Gly Asp Ile Cys Ile Gln Val Gly Gly Arg Tyr Leu Gln
                245                 250                 255
Thr Ala Phe Ala Ala Thr Arg Tyr Ala Gly Thr Glu Ala Val Leu Cys
            260                 265                 270
Val Phe Asn Asp Ile Thr Val His Cys Glu Ala Glu Thr Ala Leu Ser
        275                 280                 285
Asn Ala Lys Arg Ala Ala Asp Ala Ala Ser Gln Ala Lys Thr Leu Phe
    290                 295                 300
Leu Ala Arg Met Ser His Glu Ile Arg Thr Pro Leu Tyr Gly Val Leu
305                 310                 315                 320
Gly Thr Leu Glu Leu Leu Asp Leu Thr Thr Leu Asn Glu Arg Gln Arg
                325                 330                 335
Ala Tyr Leu Arg Thr Ile Gln Ser Ser Ser Ala Thr Leu Met Gln Leu
            340                 345                 350
Ile Ser Asp Val Leu Asp Val Ser Lys Ile Glu Ala Gly Gln Met Ala
        355                 360                 365
Leu Thr Leu Ala Ala Phe Asn Pro Leu Asp Leu Val Arg Glu Val Leu
    370                 375                 380
Gly Asn Phe Ala Ala Ser Ala Met Ala Lys Asp Leu Gln Val Asp Pro
385                 390                 395                 400
Leu Asp Thr Leu Ala Leu Glu Ala Gln Val Ala His Gly Phe Glu Glu
                405                 410                 415
Ser Val Leu Phe Glu Val Ala Gly Gly Ser Val Gly His Phe Glu Glu
            420                 425                 430
Gly Val Val Gly Val Val Glu Gln Arg Leu Gln Arg Leu Phe Gln Leu
        435                 440                 445
Gln Arg Arg Leu Val Ala His Leu His Glu Asp Asp Arg Gln Ala Pro
    450                 455                 460
```

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```
Arg Ser Gly Val Arg Arg Arg Leu Gly Ser Asp Pro Gly Gln Val His
465                 470                 475                 480
His Ile Gly Ile Val Leu His Arg Asp Ser Pro Ala Thr Leu Ala Ala
                485                 490                 495
Ala His Gly Met Ala Lys Ile Gly His Arg Gly Ser Ile Gly Val Val
            500                 505                 510
Arg Asn Val Asn Phe Gln Ala Ser Lys Thr Ser Ile Tyr Ile His Tyr
        515                 520                 525
Arg Asp Thr Phe Lys Ser Arg
    530                 535
```

7H/2

Figure 7I

ORF3-5
SEQ ID NO:38

```
Met Leu Gly Val Ala Arg Val Asp Leu Pro Glu Thr Leu Trp Trp His
 1               5                  10                  15
Asp Glu Pro Asn His Leu Ile Ile Ala Ala Ser Leu Leu Asp Leu Arg
            20                  25                  30
Arg Ile Asn Asp Phe Glu Gln Leu Val Glu Arg Pro Ala Phe Asp Ser
        35                  40                  45
Tyr Ser Leu Val Ser Pro Asp Gly Glu Val Leu Leu Gly Ala Ala Pro
    50                  55                  60
Ala Thr Gly Leu Arg Asp Gly Leu Asn Leu Thr Arg Gln Gly Val Ala
65                  70                  75                  80
Val Gln Leu Arg Ser Gln Pro Glu Asn Gly Trp Leu Ala Val Tyr Arg
                85                  90                  95
Thr Asp Tyr Gly Asn Phe Phe Arg His Ser Arg Trp Leu Val Ala Gly
            100                 105                 110
Leu Leu Leu Thr Pro Ala Leu Leu Leu Ala Gly Trp Leu Gly Met Arg
        115                 120                 125
Trp Tyr Thr Ser Ser Val Val Asn Pro Val His Arg Ala His Arg Gln
    130                 135                 140
Leu Val Glu Ser Asp Thr Phe Ser Arg Thr Leu Ile Gln Thr Ala Pro
145                 150                 155                 160
Val Ala Leu Val Val Leu Thr Gln Asp Asp Gln Gln Leu Val Thr Cys
                165                 170                 175
Asn His Leu Ala Ala Gln Trp Leu Gly Gly Pro Thr Glu Ile Leu Gly
            180                 185                 190
Leu Thr Ser Asn Trp Lys Leu Phe Asp Ala Arg Gly Gln Val Pro Gly
        195                 200                 205
Asp Ile Cys Ile Gln Val Gly Gly Arg Tyr Leu Gln Thr Ala Phe Ala
    210                 215                 220
Ala Thr Arg Tyr Ala Gly Thr Glu Ala Val Leu Cys Val Phe Asn Asp
225                 230                 235                 240
Ile Thr Val His Cys Glu Ala Glu Thr Ala Leu Ser Asn Ala Lys Arg
                245                 250                 255
Ala Ala Asp Ala Ala Ser Gln Ala Lys Thr Leu Phe Leu Ala Arg Met
            260                 265                 270
Ser His Glu Ile Arg Thr Pro Leu Tyr Gly Val Leu Gly Thr Leu Glu
        275                 280                 285
Leu Leu Asp Leu Thr Thr Leu Asn Glu Arg Gln Arg Ala Tyr Leu Arg
    290                 295                 300
Thr Ile Gln Ser Ser Ser Ala Thr Leu Met Gln Leu Ile Ser Asp Val
305                 310                 315                 320
Leu Asp Val Ser Lys Ile Glu Ala Gly Gln Met Ala Leu Thr Leu Ala
                325                 330                 335
Ala Phe Asn Pro Leu Asp Leu Val Arg Glu Val Leu Gly Asn Phe Ala
            340                 345                 350
Ala Ser Ala Met Ala Lys Asp Leu Gln Val Asp Pro Leu Asp Thr Leu
        355                 360                 365
Ala Leu Glu Ala Gln Val Ala His Gly Phe Glu Glu Ser Val Leu Phe
    370                 375                 380
Glu Val Ala Gly Gly Ser Val Gly His Phe Glu Glu Gly Val Val Gly
385                 390                 395                 400
Val Val Glu Gln Arg Leu Gln Arg Leu Phe Gln Leu Gln Arg Arg Leu
                405                 410                 415
Val Ala His Leu His Glu Asp Asp Arg Gln Ala Pro Arg Ser Gly Val
            420                 425                 430
Arg Arg Arg Leu Gly Ser Asp Pro Gly Gln Val His His Ile Gly Ile
        435                 440                 445
Val Leu His Arg Asp Ser Pro Ala Thr Leu Ala Ala Ala His Gly Met
    450                 455                 460
```

7I/1

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Ala Lys Ile Gly His Arg Gly Ser Ile Gly Val Val Arg Asn Val Asn
465                 470                 475                 480
Phe Gln Ala Ser Lys Thr Ser Ile Tyr Ile His Tyr Arg Asp Thr Phe
                485                 490                 495

Lys Ser Arg
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Figure 7J

ORF3-6
SEQ ID NO:39

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 1               5                  10                  15
Arg Gln Leu Val Glu Ser Asp Thr Phe Ser Arg Thr Leu Ile Gln Thr
            20                  25                  30
Ala Pro Val Ala Leu Val Val Leu Thr Gln Asp Asp Gln Gln Leu Val
        35                  40                  45
Thr Cys Asn His Leu Ala Ala Gln Trp Leu Gly Gly Pro Thr Glu Ile
    50                  55                  60
Leu Gly Leu Thr Ser Asn Trp Lys Leu Phe Asp Ala Arg Gly Gln Val
65                  70                  75                  80
Pro Gly Asp Ile Cys Ile Gln Val Gly Gly Arg Tyr Leu Gln Thr Ala
                85                  90                  95
Phe Ala Ala Thr Arg Tyr Ala Gly Thr Glu Ala Val Leu Cys Val Phe
            100                 105                 110
Asn Asp Ile Thr Val His Cys Glu Ala Glu Thr Ala Leu Ser Asn Ala
        115                 120                 125
Lys Arg Ala Ala Asp Ala Ala Ser Gln Ala Lys Thr Leu Phe Leu Ala
    130                 135                 140
Arg Met Ser His Glu Ile Arg Thr Pro Leu Tyr Gly Val Leu Gly Thr
145                 150                 155                 160
Leu Glu Leu Leu Asp Leu Thr Thr Leu Asn Glu Arg Gln Arg Ala Tyr
                165                 170                 175
Leu Arg Thr Ile Gln Ser Ser Ser Ala Thr Leu Met Gln Leu Ile Ser
            180                 185                 190
Asp Val Leu Asp Val Ser Lys Ile Glu Ala Gly Gln Met Ala Leu Thr
        195                 200                 205
Leu Ala Ala Phe Asn Pro Leu Asp Leu Val Arg Glu Val Leu Gly Asn
    210                 215                 220
Phe Ala Ala Ser Ala Met Ala Lys Asp Leu Gln Val Asp Pro Leu Asp
225                 230                 235                 240
Thr Leu Ala Leu Glu Ala Gln Val Ala His Gly Phe Glu Glu Ser Val
                245                 250                 255
Leu Phe Glu Val Ala Gly Gly Ser Val Gly His Phe Glu Glu Gly Val
            260                 265                 270
Val Gly Val Val Glu Gln Arg Leu Gln Arg Leu Phe Gln Leu Gln Arg
        275                 280                 285
Arg Leu Val Ala His Leu His Glu Asp Asp Arg Gln Ala Pro Arg Ser
    290                 295                 300
Gly Val Arg Arg Arg Leu Gly Ser Asp Pro Gly Gln Val His His Ile
305                 310                 315                 320
Gly Ile Val Leu His Arg Asp Ser Pro Ala Thr Leu Ala Ala Ala His
                325                 330                 335
Gly Met Ala Lys Ile Gly His Arg Gly Ser Ile Gly Val Val Arg Asn
            340                 345                 350
Val Asn Phe Gln Ala Ser Lys Thr Ser Ile Tyr Ile His Tyr Arg Asp
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Thr Phe Lys Ser Arg
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SEQUENCE LISTING

<110> The General Hospital Corporation

<120> Regulators of Biofilm Formation and Uses Thereof

<130> 00786/398WO4

<150> US 60/373,233
<151> 2002-04-16

<150> US 60/303,286
<151> 2001-07-06

<160> 39

<170> FastSEQ for Windows Version 4.0

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<211> 1200
<212> DNA
<213> Pseudomonas aeruginosa PA14

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ctgctcaacc tgtttcgcga gcgcggcgtg cagtacctgg taggtgccgg cgacggcgcg 120
gaggcgttgc gctgcctgaa gcaggacagg ttcgacctga tcctcagcga tctgatgatg 180
ccgggcatgg atggtatcca aatgatcctg caactgccgt atctcaagca tcgtccgaag 240
ctggcgctga tgagctcctc gtcgcagcgg atgatgctca gtgccagccg ggtcgcccag 300
agtctcggct tgtcggtaat cgacctgttg cccaagccga ctctgcccaa ggccatcggc 360
caacttctgg aacacctgga aagatgcctc aggcagaagc tggagccgga aaccgacgag 420
actccgcatg ggcgcacggc gttgctggat gccctgcata acgagcaact ggtgacctgg 480
ttccaggcta agaaatccct ccacaccggg cgcatagtcg gcgccgaggc gttgatacgc 540
tggagccacc cgcagcatgg cctgttgctg cccagctgtt tcatgagtga tgtcgacgct 600
accggtctgc acgaggcgtt gctctggcgc gtgctcgaac agaccctgaa cgcccaggaa 660
tcgtggcgca gggcgggtta cgagattccg gtttcggtga atctgccgcc gcacctgctc 720
gataaccagg aacttccgga tcgactctat gagtacgtcg gcgctcgcgg ggcttgtacc 780
agctcactat gtttcgagtt gaccgagagc agtgtcacaa ctctgtcaag taactactat 840
gcaggtgcct gtcgcttgcg catgaaaggg ttcggattgg cccaggacga ctttggccag 900
ggttacagct cgttctataa cctggtcacg acgcctttca cggagctgaa gatcgaccgc 960
tccctagtcc agggatgcgt agaggataac ggcctcaatg cagctgtcat cagttgtatt 1020
gagttgggtc accgcctgaa tctcgacgtg gtggccgaag gcgtggagac ctgcgaggaa 1080
ctgaatcttc ttcgtcgtct tggctgcgac cgggcgcagg gtttcctgat ttctaaggca 1140
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<210> 2
<211> 399
<212> PRT
<213> Pseudomonas aeruginosa PA14

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            20   25   30

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Leu Val Gly Ala Gly Asp Gly Ala Glu Ala Leu Arg Cys Leu Lys Gln
        35                  40                  45
Asp Arg Phe Asp Leu Ile Leu Ser Asp Leu Met Met Pro Gly Met Asp
    50                  55                  60
Gly Ile Gln Met Ile Leu Gln Leu Pro Tyr Leu Lys His Arg Pro Lys
65                  70                  75                  80
Leu Ala Leu Met Ser Ser Ser Ser Gln Arg Met Met Leu Ser Ala Ser
                85                  90                  95
Arg Val Ala Gln Ser Leu Gly Leu Ser Val Ile Asp Leu Leu Pro Lys
            100                 105                 110
Pro Thr Leu Pro Lys Ala Ile Gly Gln Leu Leu Glu His Leu Glu Arg
        115                 120                 125
Cys Leu Arg Gln Lys Leu Glu Pro Glu Thr Asp Glu Thr Pro His Gly
    130                 135                 140
Arg Thr Ala Leu Leu Asp Ala Leu His Asn Glu Gln Leu Val Thr Trp
145                 150                 155                 160
Phe Gln Ala Lys Lys Ser Leu His Thr Gly Arg Ile Val Gly Ala Glu
                165                 170                 175
Ala Leu Ile Arg Trp Ser His Pro Gln His Gly Leu Leu Leu Pro Ser
            180                 185                 190
Cys Phe Met Ser Asp Val Asp Ala Thr Gly Leu His Glu Ala Leu Leu
        195                 200                 205
Trp Arg Val Leu Glu Gln Thr Leu Asn Ala Gln Glu Ser Trp Arg Arg
    210                 215                 220
Ala Gly Tyr Glu Ile Pro Val Ser Val Asn Leu Pro Pro His Leu Leu
225                 230                 235                 240
Asp Asn Gln Glu Leu Pro Asp Arg Leu Tyr Glu Tyr Val Gly Ala Arg
                245                 250                 255
Gly Ala Cys Thr Ser Ser Leu Cys Phe Glu Leu Thr Glu Ser Ser Val
            260                 265                 270
Thr Thr Leu Ser Ser Asn Tyr Tyr Ala Gly Ala Cys Arg Leu Arg Met
        275                 280                 285
Lys Gly Phe Gly Leu Ala Gln Asp Asp Phe Gly Gln Gly Tyr Ser Ser
    290                 295                 300
Phe Tyr Asn Leu Val Thr Thr Pro Phe Thr Glu Leu Lys Ile Asp Arg
305                 310                 315                 320
Ser Leu Val Gln Gly Cys Val Glu Asp Asn Gly Leu Asn Ala Ala Val
                325                 330                 335
Ile Ser Cys Ile Glu Leu Gly His Arg Leu Asn Leu Asp Val Val Ala
            340                 345                 350
Glu Gly Val Glu Thr Cys Glu Glu Leu Asn Leu Leu Arg Arg Leu Gly
        355                 360                 365
Cys Asp Arg Ala Gln Gly Phe Leu Ile Ser Lys Ala Val Ser Ala Arg
    370                 375                 380
Glu Phe Glu Arg Gln Leu Arg Glu Asp Gly Pro Ser Leu Leu Val
385                 390                 395
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<210> 3
<211> 1416
<212> DNA
<213> Pseudomonas aeruginosa PA14

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accctgctgc aactgatcag cgatgtgctt gacgtatcca agatagaggc cggccaactg 180
gacctagagt gcgtggaatt ctccccgctg gaattgaccg aagaggtcgt gcagtcgttc 240

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accggtgccg cgcaggccaa ggggctgcag ttgtatacct gcctctctgc ggagctgccg 300
ctgcgcatgc ggggggccgc ggcgtcgatc cggcagattc tcaacaacct gctgagcaac 360
gcggtgaagt tcaccgacaa tggctatgtc aacgtccacc tgaaggccag cgtggtcgat 420
gccgaatgtg tgatgctgac ctggcaggtc aacgataccg gcatggggat caacgtcgag 480
gatcagccgc gtctgttcga accgttctac cagatacgcc gctccgagca tccggtcgca 540
ggcacgggcc tcggcttgtc gatcagccag cgcctggcgc agctaatgaa tggcagtctg 600
aaactggtca gtgagctggg gttgggcagc agctttagcc tcaggcttcc gcttgagcgg 660
atcgcgatgc aggctgagcc gcaggaccta gccgggtgcg ccgtccaagt gctggcgcct 720
gtccgcgacc taacggaatg cctgtgtggc tggatctccc gctggggtgg aagggccatg 780
gtcgcgacgc cgaggtcgct ggacgaggcg gacgcgacct cgctgctggt cgaagtgtta 840
ctgctggagg gggcgccgat gttcgaagca tggccaggat gccgggtgga gctttcccct 900
cagggtgata tggagccgca ggcacagggc cgcgactggc tgctcgggct caacaacctg 960
gacggcctgc atcgtgctct gggcctggcc catgggcgtc tcgctgatcc ttcgacgccg 1020
ccgatacggc tggctccgtt gcgcaatcta ggtctccgcg tcctagtggt ggaggataac 1080
gcgatcaacc agttgatctt gagggaccag atggaagcgc tgggctgcag cgtggagctg 1140
ctcttcgatg gtcgcgaggc gttgctgcac tgccagacgg cctgcttcga cgtggtgctc 1200
accgatatca acatgccgaa catgaacgga tacgagctaa ccgcggagct acggcgccaa 1260
gggttccggc agccgatcat cggcgcgacg gcgaacgcca tgcgtgagga gcgcgagcgc 1320
tgcatgtccg ccgggatgaa cgattgcctg gtcaaaccgg tggatctgaa tgcccttcag 1380
aactgcttga ttaatattct caaggtggat cgatga                          1416
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<210> 4
<211> 471
<212> PRT
<213> Pseudomonas aeruginosa PA14

<400> 4

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            20                  25                  30
Lys Ala Ile Gln His Ser Ser Ser Thr Leu Leu Gln Leu Ile Ser Asp
        35                  40                  45
Val Leu Asp Val Ser Lys Ile Glu Ala Gly Gln Leu Asp Leu Glu Cys
    50                  55                  60
Val Glu Phe Ser Pro Leu Glu Leu Thr Glu Glu Val Val Gln Ser Phe
65                  70                  75                  80
Thr Gly Ala Ala Gln Ala Lys Gly Leu Gln Leu Tyr Thr Cys Leu Ser
                85                  90                  95
Ala Glu Leu Pro Leu Arg Met Arg Gly Ala Ala Ala Ser Ile Arg Gln
            100                 105                 110
Ile Leu Asn Asn Leu Leu Ser Asn Ala Val Lys Phe Thr Asp Asn Gly
        115                 120                 125
Tyr Val Asn Val His Leu Lys Ala Ser Val Val Asp Ala Glu Cys Val
    130                 135                 140
Met Leu Thr Trp Gln Val Asn Asp Thr Gly Met Gly Ile Asn Val Glu
145                 150                 155                 160
Asp Gln Pro Arg Leu Phe Glu Pro Phe Tyr Gln Ile Arg Arg Ser Glu
                165                 170                 175
His Pro Val Ala Gly Thr Gly Leu Gly Leu Ser Ile Ser Gln Arg Leu
            180                 185                 190
Ala Gln Leu Met Asn Gly Ser Leu Lys Leu Val Ser Glu Leu Gly Leu
        195                 200                 205
Gly Ser Ser Phe Ser Leu Arg Leu Pro Leu Glu Arg Ile Ala Met Gln
    210                 215                 220
Ala Glu Pro Gln Asp Leu Ala Gly Cys Ala Val Gln Val Leu Ala Pro
225                 230                 235                 240
Val Arg Asp Leu Thr Glu Cys Leu Cys Gly Trp Ile Ser Arg Trp Gly
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                245                 250                 255
Gly Arg Ala Met Val Ala Thr Pro Arg Ser Leu Asp Glu Ala Asp Ala
            260                 265                 270
Thr Ser Leu Leu Val Glu Val Leu Leu Leu Glu Gly Ala Pro Met Phe
        275                 280                 285
Glu Ala Trp Pro Gly Cys Arg Val Glu Leu Ser Pro Gln Gly Asp Met
    290                 295                 300
Glu Pro Gln Ala Gln Gly Arg Asp Trp Leu Leu Gly Leu Asn Asn Leu
305                 310                 315                 320
Asp Gly Leu His Arg Ala Leu Gly Leu Ala His Gly Arg Leu Ala Asp
                325                 330                 335
Pro Ser Thr Pro Pro Ile Arg Leu Ala Pro Leu Arg Asn Leu Gly Leu
            340                 345                 350
Arg Val Leu Val Val Glu Asp Asn Ala Ile Asn Gln Leu Ile Leu Arg
        355                 360                 365
Asp Gln Met Glu Ala Leu Gly Cys Ser Val Glu Leu Leu Phe Asp Gly
    370                 375                 380
Arg Glu Ala Leu Leu His Cys Gln Thr Ala Cys Phe Asp Val Val Leu
385                 390                 395                 400
Thr Asp Ile Asn Met Pro Asn Met Asn Gly Tyr Glu Leu Thr Ala Glu
                405                 410                 415
Leu Arg Arg Gln Gly Phe Arg Gln Pro Ile Ile Gly Ala Thr Ala Asn
            420                 425                 430
Ala Met Arg Glu Glu Arg Glu Arg Cys Met Ser Ala Gly Met Asn Asp
        435                 440                 445
Cys Leu Val Lys Pro Val Asp Leu Asn Ala Leu Gln Asn Cys Leu Ile
    450                 455                 460
Asn Ile Leu Lys Val Asp Arg
465                 470
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<210> 5
<211> 1995
<212> DNA
<213> Pseudomonas aeruginosa PA14

<400> 5

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gaaaacggat tagcggtcta tgagggacgg gagttttcct ttgctatgcc atttctactg 180
gctaccaagc acgcgttgag cgccgattcc tcgggagatc cgttttcgct cggtgtattg 240
ctcgccaatt tctacggaag cttctggagt gtttccgcct atcccgcgcc acagttactg 300
atctttgatc tttccggcag cacccgcctg gcagtgccgt cgattccctc cacagcgcag 360
cgtgacaggt tgagcggaag ctatccgatg atagtcgagc gcattctggc gcgcttgcgc 420
acccggccgg tgggggagga cgctcagcgt gtccattgga tacgcgctga tcgctatcgc 480
gactcggcgc tggagatgtt gggagtcgcc cgggttgatc tgccggaaac actctggtgg 540
cacgacgagc cgaaccatct gatcatcgct gcgagcctgc ttgatctcag gcgaatcaat 600
gacttcgaac agttggttga gcgcccggca ttcgattcgt acagcctggt atcgccggat 660
ggcgaggtat tgctcggcgc ggcccctgcg accggcctga gggatggcct gaacctcacc 720
cgacaggggg tcgccgttca actgcgcagc cagcctgaga acggctggct cgcggtctac 780
cgaaccgact acggcaattt ctttcgccac tcccggtggc tggtggcagg tctgctgctg 840
accccggcgc tgctcctggc cggttggctc gggatgcgtt ggtacaccag cagcgtcgtc 900
aacccggtgc atcgggcgca ccggcaactg gtggagagcg acaccttcag ccggacgctg 960
atacagaccg cgccggtggc tctggtggtg ctgacccagg atgaccagca actggtgacc 1020
tgcaaccact tggccgccca gtggctgggc gggcccacgg agatccttgg gctgacttcc 1080
aactggaagc ttttcgatgc gcgtgggcag gtaccaggag acatctgtat ccaggtcggt 1140
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ttcaaatcta gatag                                                  1995
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<210> 6
<211> 664
<212> PRT
<213> Pseudomonas aeruginosa PA14

<400> 6

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            20                  25                  30
Leu Gln Arg His Leu Leu Ala Lys Glu Asn Gly Leu Ala Val Tyr Glu
        35                  40                  45
Gly Arg Glu Phe Ser Phe Ala Met Pro Phe Leu Leu Ala Thr Lys His
    50                  55                  60
Ala Leu Ser Ala Asp Ser Ser Gly Asp Pro Phe Ser Leu Gly Val Leu
65                  70                  75                  80
Leu Ala Asn Phe Tyr Gly Ser Phe Trp Ser Val Ser Ala Tyr Pro Ala
                85                  90                  95
Pro Gln Leu Leu Ile Phe Asp Leu Ser Gly Ser Thr Arg Leu Ala Val
            100                 105                 110
Pro Ser Ile Pro Ser Thr Ala Gln Arg Asp Arg Leu Ser Gly Ser Tyr
        115                 120                 125
Pro Met Ile Val Glu Arg Ile Leu Ala Arg Leu Arg Thr Arg Pro Val
    130                 135                 140
Gly Glu Asp Ala Gln Arg Val His Trp Ile Arg Ala Asp Arg Tyr Arg
145                 150                 155                 160
Asp Ser Ala Leu Glu Met Leu Gly Val Ala Arg Val Asp Leu Pro Glu
                165                 170                 175
Thr Leu Trp Trp His Asp Glu Pro Asn His Leu Ile Ile Ala Ala Ser
            180                 185                 190
Leu Leu Asp Leu Arg Arg Ile Asn Asp Phe Glu Gln Leu Val Glu Arg
        195                 200                 205
Pro Ala Phe Asp Ser Tyr Ser Leu Val Ser Pro Asp Gly Glu Val Leu
    210                 215                 220
Leu Gly Ala Ala Pro Ala Thr Gly Leu Arg Asp Gly Leu Asn Leu Thr
225                 230                 235                 240
Arg Gln Gly Val Ala Val Gln Leu Arg Ser Gln Pro Glu Asn Gly Trp
                245                 250                 255
Leu Ala Val Tyr Arg Thr Asp Tyr Gly Asn Phe Phe Arg His Ser Arg
            260                 265                 270
Trp Leu Val Ala Gly Leu Leu Leu Thr Pro Ala Leu Leu Leu Ala Gly
        275                 280                 285
Trp Leu Gly Met Arg Trp Tyr Thr Ser Ser Val Val Asn Pro Val His
    290                 295                 300
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Arg Ala His Arg Gln Leu Val Glu Ser Asp Thr Phe Ser Arg Thr Leu
305                 310                 315                 320
Ile Gln Thr Ala Pro Val Ala Leu Val Val Leu Thr Gln Asp Asp Gln
                325                 330                 335
Gln Leu Val Thr Cys Asn His Leu Ala Ala Gln Trp Leu Gly Gly Pro
            340                 345                 350
Thr Glu Ile Leu Gly Leu Thr Ser Asn Trp Lys Leu Phe Asp Ala Arg
        355                 360                 365
Gly Gln Val Pro Gly Asp Ile Cys Ile Gln Val Gly Gly Arg Tyr Leu
    370                 375                 380
Gln Thr Ala Phe Ala Ala Thr Arg Tyr Ala Gly Thr Glu Ala Val Leu
385                 390                 395                 400
Cys Val Phe Asn Asp Ile Thr Val His Cys Glu Ala Glu Thr Ala Leu
                405                 410                 415
Ser Asn Ala Lys Arg Ala Ala Asp Ala Ala Ser Gln Ala Lys Thr Leu
            420                 425                 430
Phe Leu Ala Arg Met Ser His Glu Ile Arg Thr Pro Leu Tyr Gly Val
        435                 440                 445
Leu Gly Thr Leu Glu Leu Leu Asp Leu Thr Thr Leu Asn Glu Arg Gln
    450                 455                 460
Arg Ala Tyr Leu Arg Thr Ile Gln Ser Ser Ser Ala Thr Leu Met Gln
465                 470                 475                 480
Leu Ile Ser Asp Val Leu Asp Val Ser Lys Ile Glu Ala Gly Gln Met
                485                 490                 495
Ala Leu Thr Leu Ala Ala Phe Asn Pro Leu Asp Leu Val Arg Glu Val
            500                 505                 510
Leu Gly Asn Phe Ala Ala Ser Ala Met Ala Lys Asp Leu Gln Val Asp
        515                 520                 525
Pro Leu Asp Thr Leu Ala Leu Glu Ala Gln Val Ala His Gly Phe Glu
    530                 535                 540
Glu Ser Val Leu Phe Glu Val Ala Gly Gly Ser Val Gly His Phe Glu
545                 550                 555                 560
Glu Gly Val Val Gly Val Val Glu Gln Arg Leu Gln Arg Leu Phe Gln
                565                 570                 575
Leu Gln Arg Arg Leu Val Ala His Leu His Glu Asp Asp Arg Gln Ala
            580                 585                 590
Pro Arg Ser Gly Val Arg Arg Arg Leu Gly Ser Asp Pro Gly Gln Val
        595                 600                 605
His His Ile Gly Ile Val Leu His Arg Asp Ser Pro Ala Thr Leu Ala
    610                 615                 620
Ala Ala His Gly Met Ala Lys Ile Gly His Arg Gly Ser Ile Gly Val
625                 630                 635                 640
Val Arg Asn Val Asn Phe Gln Ala Ser Lys Thr Ser Ile Tyr Ile His
                645                 650                 655
Tyr Arg Asp Thr Phe Lys Ser Arg
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<210> 7
<211> 6410
<212> DNA
<213> Pseudomonas aeruginosa PA14

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ggcatgaagt tgaagaattt cttacagcct tttgatagcg gtttctccac tccgagtgct 180
gcgctcaagc tgctccgcat gctcggtggc gccttgatgt tgtgcgtgct atgcagcctg 240

atattcagtg tgagcatggt tttaaaccat caggtgtccc tcagtcggca agctatgaat 300
gtggctatgt acgaagcgca gctttatttc gagcagcgcg aggcgttgct caatcacttg 360
agcggcaatg tcgtgccctt ggccgcgggt agagcgctcg tcaacgaagc gccgaacaat 420
gtgagcatcc tgccgttgag tgacggaggg cgaggtctgc tattgaccgc tcgcacgctc 480
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acggcctgct tcgacgtggt gctcaccgat atcaacatgc cgaacatgaa cggatacgag 1980
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gccatgcgtg aggagcgcga gcgctgcatg tccgccggga tgaacgattg cctggtcaaa 2100
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<210> 16
<211> 2130
<212> DNA
<213> Pseudomonas aeruginosa PA14

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ccgcagcata tggtgctttt ccagcacgtg gggtcttcga gctgggatct gatctatcac 180
atcggtatcg gtcgcctgtt gctggctctg tggctccctc tgttacttgc ctctgcgttg 240

gcactcgcag tcggcatcct actgcattgg ctggtgcgga gcatcgagcg acgcttgata 300
gagcccgcaa agcgacgcct tgaagcattg aaggagagcg aagccttttc ccgtgcagtt 360
atccaggccg cgcccgtcgc gctgtgcgtg ctgcgtcgtg ccgacgccgc agtggtcctg 420
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agatggattt cccaggcgtt cgcaggaggt gtgaagtgtt ctggagaaga actggaaacc 540
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gcaaaatccc tggcggatgc tgccaatgaa gccaagacgc tgtttctcgc caccatgagc 720
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gagctgagtc ggcagcaggc cggttaccta aaggcaatcc agcattcctc gtcgaccctg 840
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gccgcgcagg ccaaggggct gcagttgtat acctgcctct ctgcggagct gccgctgcgc 1020
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aagttcaccg acaatggcta tgtcaacgtc cacctgaagg ccagcgtggt cgatgccgaa 1140
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acgccgaggt cgctggacga ggcggacgcg acctcgctgc tggtcgaagt gttactgctg 1560
gaggggcgc cgatgttcga agcatggcca ggatgccggg tggagctttc ccctcagggt 1620
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gatggtcgcg aggcgttgct gcactgccag acggcctgct tcgacgtggt gctcaccgat 1920
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cggcagccga tcatcggcgc gacggcgaac gccatgcgtg aggagcgcga gcgctgcatg 2040
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<210> 17
<211> 2001
<212> DNA
<213> Pseudimonas aeruginosa PA14

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gtcggcatcc tactgcattg gctggtgcgg agcatcgagc gacgcttgat agagcccgca 180
aagcgacgcc ttgaagcatt gaaggagagc gaagcctttt cccgtgcagt tatccaggcc 240
gcgcccgtcg cgctgtgcgt gctgcgtcgt gccgacgccg cagtggtcct ggaaaatccc 300
caggcgcgcc aatggctggg tgatagcgag gcgattgccc acgacgcgcc gagatggatt 360
tcccaggcgt tcgcaggagg tgtgaagtgt tctggagaag aactggaaac cgaggcaggg 420
ctacatcttc atctcaatta cacgcccacc cgctataacg gtgaagacgt attgttctgc 480
gccttcagtg aaatcagtgc acgcaagcgg atggaggcgg aactggctcg cgcaaaatcc 540
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cggcagcagg ccggttacct aaaggcaatc cagcattcct cgtcgaccct gctgcaactg 720
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atcatcggcg cgacggcgaa cgccatgcgt gaggagcgcg agcgctgcat gtccgccggg 1920
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<210> 18
<211> 1491
<212> DNA
<213> Pseudomonas aeruginosa PA14

<400> 18
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cttgagctgc ttgggcgtac cgagctgagt cggcagcagg ccggttacct aaaggcaatc 180
cagcattcct cgtcgaccct gctgcaactg atcagcgatg tgcttgacgt atccaagata 240
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gaggagcgcg agcgctgcat gtccgccggg atgaacgatt gcctggtcaa accggtggat 1440
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<210> 19
<211> 931
<212> PRT
<213> Pseudomonas aeruginosa PA14

<400> 19
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Pro Ser Ala Ala Leu Lys Leu Leu Arg Met Leu Gly Gly Ala Leu Met
20 25 30

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Leu Cys Val Leu Cys Ser Leu Ile Phe Ser Val Ser Met Val Leu Asn
        35                  40                  45
His Gln Val Ser Leu Ser Arg Gln Ala Met Asn Val Ala Met Tyr Glu
    50                  55                  60
Ala Gln Leu Tyr Phe Glu Gln Arg Glu Ala Leu Leu Asn His Leu Ser
65                  70                  75                  80
Gly Asn Val Val Pro Leu Ala Ala Gly Arg Ala Leu Val Asn Glu Ala
                85                  90                  95
Pro Asn Asn Val Ser Ile Leu Pro Leu Ser Asp Gly Gly Arg Gly Leu
            100                 105                 110
Leu Leu Thr Ala Arg Thr Leu Gly Asp Leu Arg Glu Lys Arg Leu Ala
        115                 120                 125
Leu Met Tyr Leu Val Asp Thr Asp Lys Gly Pro Leu Val Tyr Arg Leu
    130                 135                 140
Thr Ala Asp Gly Arg Pro Ser Ala Ala Ile Ser Ser Thr Ile Thr Lys
145                 150                 155                 160
Glu Val Tyr Arg Ala Leu Leu Ala Thr Pro Ser Ala Pro Val His Trp
                165                 170                 175
Val Thr Asp Gly Gly Thr Pro Gln Arg Leu Tyr Leu Phe Glu Ser Leu
            180                 185                 190
Gly Asp Glu Pro Gly Glu Gly Trp Leu Gly Leu Glu Ile Leu Gly Glu
        195                 200                 205
Asp Leu Asp Ser Met Leu Arg Arg Asn Asp Ala Gly Asn Tyr Met Leu
    210                 215                 220
Leu Asp Gln His Gly Gln Val Val Leu Ala Thr Asp Ala Glu Ala Leu
225                 230                 235                 240
Gly Ser Gly Ala Ser Arg Thr Leu Leu Arg Gly Asp Gly Phe Gly Phe
                245                 250                 255
Ile Gly Ala Gly Pro Leu Pro Gln His Met Val Leu Phe Gln His Val
            260                 265                 270
Gly Ser Ser Ser Trp Asp Leu Ile Tyr His Ile Gly Ile Gly Arg Leu
        275                 280                 285
Leu Leu Ala Leu Trp Leu Pro Leu Leu Leu Ala Ser Ala Leu Ala Leu
    290                 295                 300
Ala Val Gly Ile Leu Leu His Trp Leu Val Arg Ser Ile Glu Arg Arg
305                 310                 315                 320
Leu Ile Glu Pro Ala Lys Arg Arg Leu Glu Ala Leu Lys Glu Ser Glu
                325                 330                 335
Ala Phe Ser Arg Ala Val Ile Gln Ala Ala Pro Val Ala Leu Cys Val
            340                 345                 350
Leu Arg Arg Ala Asp Ala Ala Val Val Leu Glu Asn Pro Gln Ala Arg
        355                 360                 365
Gln Trp Leu Gly Asp Ser Glu Ala Ile Ala His Asp Ala Pro Arg Trp
    370                 375                 380
Ile Ser Gln Ala Phe Ala Gly Gly Val Lys Cys Ser Gly Glu Glu Leu
385                 390                 395                 400
Glu Thr Glu Ala Gly Leu His Leu His Leu Asn Tyr Thr Pro Thr Arg
                405                 410                 415
Tyr Asn Gly Glu Asp Val Leu Phe Cys Ala Phe Ser Glu Ile Ser Ala
            420                 425                 430
Arg Lys Arg Met Glu Ala Glu Leu Ala Arg Ala Lys Ser Leu Ala Asp
        435                 440                 445
Ala Ala Asn Glu Ala Lys Thr Leu Phe Leu Ala Thr Met Ser His Glu
    450                 455                 460
Ile Arg Thr Pro Leu Tyr Gly Met Leu Gly Thr Leu Glu Leu Leu Gly
465                 470                 475                 480
Arg Thr Glu Leu Ser Arg Gln Gln Ala Gly Tyr Leu Lys Ala Ile Gln
                485                 490                 495
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His Ser Ser Ser Thr Leu Leu Gln Leu Ile Ser Asp Val Leu Asp Val
            500                 505                 510
Ser Lys Ile Glu Ala Gly Gln Leu Asp Leu Glu Cys Val Glu Phe Ser
        515                 520                 525
Pro Leu Glu Leu Thr Glu Glu Val Val Gln Ser Phe Thr Gly Ala Ala
    530                 535                 540
Gln Ala Lys Gly Leu Gln Leu Tyr Thr Cys Leu Ser Ala Glu Leu Pro
545                 550                 555                 560
Leu Arg Met Arg Gly Ala Ala Ala Ser Ile Arg Gln Ile Leu Asn Asn
                565                 570                 575
Leu Leu Ser Asn Ala Val Lys Phe Thr Asp Asn Gly Tyr Val Asn Val
            580                 585                 590
His Leu Lys Ala Ser Val Val Asp Ala Glu Cys Val Met Leu Thr Trp
        595                 600                 605
Gln Val Asn Asp Thr Gly Met Gly Ile Asn Val Glu Asp Gln Pro Arg
    610                 615                 620
Leu Phe Glu Pro Phe Tyr Gln Ile Arg Arg Ser Glu His Pro Val Ala
625                 630                 635                 640
Gly Thr Gly Leu Gly Leu Ser Ile Ser Gln Arg Leu Ala Gln Leu Met
                645                 650                 655
Asn Gly Ser Leu Lys Leu Val Ser Glu Leu Gly Leu Gly Ser Ser Phe
            660                 665                 670
Ser Leu Arg Leu Pro Leu Glu Arg Ile Ala Met Gln Ala Glu Pro Gln
        675                 680                 685
Asp Leu Ala Gly Cys Ala Val Gln Val Leu Ala Pro Val Arg Asp Leu
    690                 695                 700
Thr Glu Cys Leu Cys Gly Trp Ile Ser Arg Trp Gly Gly Arg Ala Met
705                 710                 715                 720
Val Ala Thr Pro Arg Ser Leu Asp Glu Ala Asp Ala Thr Ser Leu Leu
                725                 730                 735
Val Glu Val Leu Leu Leu Glu Gly Ala Pro Met Phe Glu Ala Trp Pro
            740                 745                 750
Gly Cys Arg Val Glu Leu Ser Pro Gln Gly Asp Met Glu Pro Gln Ala
        755                 760                 765
Gln Gly Arg Asp Trp Leu Leu Gly Leu Asn Asn Leu Asp Gly Leu His
    770                 775                 780
Arg Ala Leu Gly Leu Ala His Gly Arg Leu Ala Asp Pro Ser Thr Pro
785                 790                 795                 800
Pro Ile Arg Leu Ala Pro Leu Arg Asn Leu Gly Leu Arg Val Leu Val
                805                 810                 815
Val Glu Asp Asn Ala Ile Asn Gln Leu Ile Leu Arg Asp Gln Met Glu
            820                 825                 830
Ala Leu Gly Cys Ser Val Glu Leu Leu Phe Asp Gly Arg Glu Ala Leu
        835                 840                 845
Leu His Cys Gln Thr Ala Cys Phe Asp Val Val Leu Thr Asp Ile Asn
    850                 855                 860
Met Pro Asn Met Asn Gly Tyr Glu Leu Thr Ala Glu Leu Arg Arg Gln
865                 870                 875                 880
Gly Phe Arg Gln Pro Ile Ile Gly Ala Thr Ala Asn Ala Met Arg Glu
                885                 890                 895
Glu Arg Glu Arg Cys Met Ser Ala Gly Met Asn Asp Cys Leu Val Lys
            900                 905                 910
Pro Val Asp Leu Asn Ala Leu Gln Asn Cys Leu Ile Asn Ile Leu Lys
        915                 920                 925
Val Asp Arg
    930
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<210> 20
<211> 906
<212> PRT
<213> Pseudomonas aeruginosa PA14

<400> 20

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Ser Val Ser Met Val Leu Asn His Gln Val Ser Leu Ser Arg Gln Ala
            20                  25                  30
Met Asn Val Ala Met Tyr Glu Ala Gln Leu Tyr Phe Glu Gln Arg Glu
        35                  40                  45
Ala Leu Leu Asn His Leu Ser Gly Asn Val Val Pro Leu Ala Ala Gly
    50                  55                  60
Arg Ala Leu Val Asn Glu Ala Pro Asn Asn Val Ser Ile Leu Pro Leu
65                  70                  75                  80
Ser Asp Gly Gly Arg Gly Leu Leu Leu Thr Ala Arg Thr Leu Gly Asp
                85                  90                  95
Leu Arg Glu Lys Arg Leu Ala Leu Met Tyr Leu Val Asp Thr Asp Lys
            100                 105                 110
Gly Pro Leu Val Tyr Arg Leu Thr Ala Asp Gly Arg Pro Ser Ala Ala
        115                 120                 125
Ile Ser Ser Thr Ile Thr Lys Glu Val Tyr Arg Ala Leu Leu Ala Thr
    130                 135                 140
Pro Ser Ala Pro Val His Trp Val Thr Asp Gly Gly Thr Pro Gln Arg
145                 150                 155                 160
Leu Tyr Leu Phe Glu Ser Leu Gly Asp Glu Pro Gly Glu Gly Trp Leu
                165                 170                 175
Gly Leu Glu Ile Leu Gly Glu Asp Leu Asp Ser Met Leu Arg Arg Asn
            180                 185                 190
Asp Ala Gly Asn Tyr Met Leu Leu Asp Gln His Gly Gln Val Val Leu
        195                 200                 205
Ala Thr Asp Ala Glu Ala Leu Gly Ser Gly Ala Ser Arg Thr Leu Leu
    210                 215                 220
Arg Gly Asp Gly Phe Gly Phe Ile Gly Ala Gly Pro Leu Pro Gln His
225                 230                 235                 240
Met Val Leu Phe Gln His Val Gly Ser Ser Ser Trp Asp Leu Ile Tyr
                245                 250                 255
His Ile Gly Ile Gly Arg Leu Leu Leu Ala Leu Trp Leu Pro Leu Leu
            260                 265                 270
Leu Ala Ser Ala Leu Ala Leu Ala Val Gly Ile Leu Leu His Trp Leu
        275                 280                 285
Val Arg Ser Ile Glu Arg Arg Leu Ile Glu Pro Ala Lys Arg Arg Leu
    290                 295                 300
Glu Ala Leu Lys Glu Ser Glu Ala Phe Ser Arg Ala Val Ile Gln Ala
305                 310                 315                 320
Ala Pro Val Ala Leu Cys Val Leu Arg Arg Ala Asp Ala Ala Val Val
                325                 330                 335
Leu Glu Asn Pro Gln Ala Arg Gln Trp Leu Gly Asp Ser Glu Ala Ile
            340                 345                 350
Ala His Asp Ala Pro Arg Trp Ile Ser Gln Ala Phe Ala Gly Gly Val
        355                 360                 365
Lys Cys Ser Gly Glu Glu Leu Glu Thr Glu Ala Gly Leu His Leu His
    370                 375                 380
Leu Asn Tyr Thr Pro Thr Arg Tyr Asn Gly Glu Asp Val Leu Phe Cys
385                 390                 395                 400
Ala Phe Ser Glu Ile Ser Ala Arg Lys Arg Met Glu Ala Glu Leu Ala
                405                 410                 415
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Arg Ala Lys Ser Leu Ala Asp Ala Ala Asn Glu Ala Lys Thr Leu Phe
            420                 425                 430
Leu Ala Thr Met Ser His Glu Ile Arg Thr Pro Leu Tyr Gly Met Leu
        435                 440                 445
Gly Thr Leu Glu Leu Leu Gly Arg Thr Glu Leu Ser Arg Gln Gln Ala
    450                 455                 460
Gly Tyr Leu Lys Ala Ile Gln His Ser Ser Ser Thr Leu Leu Gln Leu
465                 470                 475                 480
Ile Ser Asp Val Leu Asp Val Ser Lys Ile Glu Ala Gly Gln Leu Asp
                485                 490                 495
Leu Glu Cys Val Glu Phe Ser Pro Leu Glu Leu Thr Glu Glu Val Val
            500                 505                 510
Gln Ser Phe Thr Gly Ala Ala Gln Ala Lys Gly Leu Gln Leu Tyr Thr
        515                 520                 525
Cys Leu Ser Ala Glu Leu Pro Leu Arg Met Arg Gly Ala Ala Ala Ser
    530                 535                 540
Ile Arg Gln Ile Leu Asn Asn Leu Leu Ser Asn Ala Val Lys Phe Thr
545                 550                 555                 560
Asp Asn Gly Tyr Val Asn Val His Leu Lys Ala Ser Val Val Asp Ala
                565                 570                 575
Glu Cys Val Met Leu Thr Trp Gln Val Asn Asp Thr Gly Met Gly Ile
            580                 585                 590
Asn Val Glu Asp Gln Pro Arg Leu Phe Glu Pro Phe Tyr Gln Ile Arg
        595                 600                 605
Arg Ser Glu His Pro Val Ala Gly Thr Gly Leu Gly Leu Ser Ile Ser
    610                 615                 620
Gln Arg Leu Ala Gln Leu Met Asn Gly Ser Leu Lys Leu Val Ser Glu
625                 630                 635                 640
Leu Gly Leu Gly Ser Ser Phe Ser Leu Arg Leu Pro Leu Glu Arg Ile
                645                 650                 655
Ala Met Gln Ala Glu Pro Gln Asp Leu Ala Gly Cys Ala Val Gln Val
            660                 665                 670
Leu Ala Pro Val Arg Asp Leu Thr Glu Cys Leu Cys Gly Trp Ile Ser
        675                 680                 685
Arg Trp Gly Gly Arg Ala Met Val Ala Thr Pro Arg Ser Leu Asp Glu
    690                 695                 700
Ala Asp Ala Thr Ser Leu Leu Val Glu Val Leu Leu Leu Glu Gly Ala
705                 710                 715                 720
Pro Met Phe Glu Ala Trp Pro Gly Cys Arg Val Glu Leu Ser Pro Gln
                725                 730                 735
Gly Asp Met Glu Pro Gln Ala Gln Gly Arg Asp Trp Leu Leu Gly Leu
            740                 745                 750
Asn Asn Leu Asp Gly Leu His Arg Ala Leu Gly Leu Ala His Gly Arg
        755                 760                 765
Leu Ala Asp Pro Ser Thr Pro Pro Ile Arg Leu Ala Pro Leu Arg Asn
    770                 775                 780
Leu Gly Leu Arg Val Leu Val Val Glu Asp Asn Ala Ile Asn Gln Leu
785                 790                 795                 800
Ile Leu Arg Asp Gln Met Glu Ala Leu Gly Cys Ser Val Glu Leu Leu
                805                 810                 815
Phe Asp Gly Arg Glu Ala Leu Leu His Cys Gln Thr Ala Cys Phe Asp
            820                 825                 830
Val Val Leu Thr Asp Ile Asn Met Pro Asn Met Asn Gly Tyr Glu Leu
        835                 840                 845
Thr Ala Glu Leu Arg Arg Gln Gly Phe Arg Gln Pro Ile Ile Gly Ala
    850                 855                 860
Thr Ala Asn Ala Met Arg Glu Glu Arg Glu Arg Cys Met Ser Ala Gly
865                 870                 875                 880
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Met Asn Asp Cys Leu Val Lys Pro Val Asp Leu Asn Ala Leu Gln Asn
885 890 895
Cys Leu Ile Asn Ile Leu Lys Val Asp Arg
900 905

<210> 21
<211> 900
<212> PRT
<213> Pseudomonas aeruginosa PA14

<400> 21
Met Leu Cys Val Leu Cys Ser Leu Ile Phe Ser Val Ser Met Val Leu
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Asn His Gln Val Ser Leu Ser Arg Gln Ala Met Asn Val Ala Met Tyr
20 25 30
Glu Ala Gln Leu Tyr Phe Glu Gln Arg Glu Ala Leu Leu Asn His Leu
35 40 45
Ser Gly Asn Val Val Pro Leu Ala Ala Gly Arg Ala Leu Val Asn Glu
50 55 60
Ala Pro Asn Asn Val Ser Ile Leu Pro Leu Ser Asp Gly Gly Arg Gly
65 70 75 80
Leu Leu Leu Thr Ala Arg Thr Leu Gly Asp Leu Arg Glu Lys Arg Leu
85 90 95
Ala Leu Met Tyr Leu Val Asp Thr Asp Lys Gly Pro Leu Val Tyr Arg
100 105 110
Leu Thr Ala Asp Gly Arg Pro Ser Ala Ala Ile Ser Ser Thr Ile Thr
115 120 125
Lys Glu Val Tyr Arg Ala Leu Leu Ala Thr Pro Ser Ala Pro Val His
130 135 140
Trp Val Thr Asp Gly Gly Thr Pro Gln Arg Leu Tyr Leu Phe Glu Ser
145 150 155 160
Leu Gly Asp Glu Pro Gly Glu Gly Trp Leu Gly Leu Glu Ile Leu Gly
165 170 175
Glu Asp Leu Asp Ser Met Leu Arg Arg Asn Asp Ala Gly Asn Tyr Met
180 185 190
Leu Leu Asp Gln His Gly Gln Val Val Leu Ala Thr Asp Ala Glu Ala
195 200 205
Leu Gly Ser Gly Ala Ser Arg Thr Leu Leu Arg Gly Asp Gly Phe Gly
210 215 220
Phe Ile Gly Ala Gly Pro Leu Pro Gln His Met Val Leu Phe Gln His
225 230 235 240
Val Gly Ser Ser Ser Trp Asp Leu Ile Tyr His Ile Gly Ile Gly Arg
245 250 255
Leu Leu Leu Ala Leu Trp Leu Pro Leu Leu Leu Ala Ser Ala Leu Ala
260 265 270
Leu Ala Val Gly Ile Leu Leu His Trp Leu Val Arg Ser Ile Glu Arg
275 280 285
Arg Leu Ile Glu Pro Ala Lys Arg Arg Leu Glu Ala Leu Lys Glu Ser
290 295 300
Glu Ala Phe Ser Arg Ala Val Ile Gln Ala Ala Pro Val Ala Leu Cys
305 310 315 320
Val Leu Arg Arg Ala Asp Ala Ala Val Val Leu Glu Asn Pro Gln Ala
325 330 335
Arg Gln Trp Leu Gly Asp Ser Glu Ala Ile Ala His Asp Ala Pro Arg
340 345 350
Trp Ile Ser Gln Ala Phe Ala Gly Gly Val Lys Cys Ser Gly Glu Glu
355 360 365

```
Leu Glu Thr Glu Ala Gly Leu His Leu His Leu Asn Tyr Thr Pro Thr
    370                 375                 380
Arg Tyr Asn Gly Glu Asp Val Leu Phe Cys Ala Phe Ser Glu Ile Ser
385                 390                 395                 400
Ala Arg Lys Arg Met Glu Ala Glu Leu Ala Arg Ala Lys Ser Leu Ala
                405                 410                 415
Asp Ala Ala Asn Glu Ala Lys Thr Leu Phe Leu Ala Thr Met Ser His
            420                 425                 430
Glu Ile Arg Thr Pro Leu Tyr Gly Met Leu Gly Thr Leu Glu Leu Leu
        435                 440                 445
Gly Arg Thr Glu Leu Ser Arg Gln Gln Ala Gly Tyr Leu Lys Ala Ile
    450                 455                 460
Gln His Ser Ser Ser Thr Leu Leu Gln Leu Ile Ser Asp Val Leu Asp
465                 470                 475                 480
Val Ser Lys Ile Glu Ala Gly Gln Leu Asp Leu Glu Cys Val Glu Phe
                485                 490                 495
Ser Pro Leu Glu Leu Thr Glu Glu Val Val Gln Ser Phe Thr Gly Ala
            500                 505                 510
Ala Gln Ala Lys Gly Leu Gln Leu Tyr Thr Cys Leu Ser Ala Glu Leu
        515                 520                 525
Pro Leu Arg Met Arg Gly Ala Ala Ala Ser Ile Arg Gln Ile Leu Asn
    530                 535                 540
Asn Leu Leu Ser Asn Ala Val Lys Phe Thr Asp Asn Gly Tyr Val Asn
545                 550                 555                 560
Val His Leu Lys Ala Ser Val Val Asp Ala Glu Cys Val Met Leu Thr
                565                 570                 575
Trp Gln Val Asn Asp Thr Gly Met Gly Ile Asn Val Glu Asp Gln Pro
            580                 585                 590
Arg Leu Phe Glu Pro Phe Tyr Gln Ile Arg Arg Ser Glu His Pro Val
        595                 600                 605
Ala Gly Thr Gly Leu Gly Leu Ser Ile Ser Gln Arg Leu Ala Gln Leu
    610                 615                 620
Met Asn Gly Ser Leu Lys Leu Val Ser Glu Leu Gly Leu Gly Ser Ser
625                 630                 635                 640
Phe Ser Leu Arg Leu Pro Leu Glu Arg Ile Ala Met Gln Ala Glu Pro
                645                 650                 655
Gln Asp Leu Ala Gly Cys Ala Val Gln Val Leu Ala Pro Val Arg Asp
            660                 665                 670
Leu Thr Glu Cys Leu Cys Gly Trp Ile Ser Arg Trp Gly Gly Arg Ala
        675                 680                 685
Met Val Ala Thr Pro Arg Ser Leu Asp Glu Ala Asp Ala Thr Ser Leu
    690                 695                 700
Leu Val Glu Val Leu Leu Glu Gly Ala Pro Met Phe Glu Ala Trp
705                 710                 715                 720
Pro Gly Cys Arg Val Glu Leu Ser Pro Gln Gly Asp Met Glu Pro Gln
                725                 730                 735
Ala Gln Gly Arg Asp Trp Leu Leu Gly Leu Asn Asn Leu Asp Gly Leu
            740                 745                 750
His Arg Ala Leu Gly Leu Ala His Gly Arg Leu Ala Asp Pro Ser Thr
        755                 760                 765
Pro Pro Ile Arg Leu Ala Pro Leu Arg Asn Leu Gly Leu Arg Val Leu
    770                 775                 780
Val Val Glu Asp Asn Ala Ile Asn Gln Leu Ile Leu Arg Asp Gln Met
785                 790                 795                 800
Glu Ala Leu Gly Cys Ser Val Glu Leu Leu Phe Asp Gly Arg Glu Ala
                805                 810                 815
Leu Leu His Cys Gln Thr Ala Cys Phe Asp Val Val Leu Thr Asp Ile
            820                 825                 830
```

```
Asn Met Pro Asn Met Asn Gly Tyr Glu Leu Thr Ala Glu Leu Arg Arg
        835                 840                 845
Gln Gly Phe Arg Gln Pro Ile Ile Gly Ala Thr Ala Asn Ala Met Arg
    850                 855                 860
Glu Glu Arg Glu Arg Cys Met Ser Ala Gly Met Asn Asp Cys Leu Val
865                 870                 875                 880
Lys Pro Val Asp Leu Asn Ala Leu Gln Asn Cys Leu Ile Asn Ile Leu
                885                 890                 895
Lys Val Asp Arg
            900
```

<210> 22
<211> 887
<212> PRT
<213> Pseudomonas aeruginosa PA14

```
<400> 22
Met Val Leu Asn His Gln Val Ser Leu Ser Arg Gln Ala Met Asn Val
 1               5                  10                  15
Ala Met Tyr Glu Ala Gln Leu Tyr Phe Glu Gln Arg Glu Ala Leu Leu
            20                  25                  30
Asn His Leu Ser Gly Asn Val Val Pro Leu Ala Ala Gly Arg Ala Leu
        35                  40                  45
Val Asn Glu Ala Pro Asn Asn Val Ser Ile Leu Pro Leu Ser Asp Gly
    50                  55                  60
Gly Arg Gly Leu Leu Leu Thr Ala Arg Thr Leu Gly Asp Leu Arg Glu
65                  70                  75                  80
Lys Arg Leu Ala Leu Met Tyr Leu Val Asp Thr Asp Lys Gly Pro Leu
                85                  90                  95
Val Tyr Arg Leu Thr Ala Asp Gly Arg Pro Ser Ala Ala Ile Ser Ser
            100                 105                 110
Thr Ile Thr Lys Glu Val Tyr Arg Ala Leu Leu Ala Thr Pro Ser Ala
        115                 120                 125
Pro Val His Trp Val Thr Asp Gly Gly Thr Pro Gln Arg Leu Tyr Leu
    130                 135                 140
Phe Glu Ser Leu Gly Asp Glu Pro Gly Glu Gly Trp Leu Gly Leu Glu
145                 150                 155                 160
Ile Leu Gly Glu Asp Leu Asp Ser Met Leu Arg Arg Asn Asp Ala Gly
                165                 170                 175
Asn Tyr Met Leu Leu Asp Gln His Gly Gln Val Val Leu Ala Thr Asp
            180                 185                 190
Ala Glu Ala Leu Gly Ser Gly Ala Ser Arg Thr Leu Leu Arg Gly Asp
        195                 200                 205
Gly Phe Gly Phe Ile Gly Ala Gly Pro Leu Pro Gln His Met Val Leu
    210                 215                 220
Phe Gln His Val Gly Ser Ser Ser Trp Asp Leu Ile Tyr His Ile Gly
225                 230                 235                 240
Ile Gly Arg Leu Leu Leu Ala Leu Trp Leu Pro Leu Leu Leu Ala Ser
                245                 250                 255
Ala Leu Ala Leu Ala Val Gly Ile Leu Leu His Trp Leu Val Arg Ser
            260                 265                 270
Ile Glu Arg Arg Leu Ile Glu Pro Ala Lys Arg Arg Leu Glu Ala Leu
        275                 280                 285
Lys Glu Ser Glu Ala Phe Ser Arg Ala Val Ile Gln Ala Ala Pro Val
    290                 295                 300
Ala Leu Cys Val Leu Arg Arg Ala Asp Ala Ala Val Val Leu Glu Asn
305                 310                 315                 320
```

Pro Gln Ala Arg Gln Trp Leu Gly Asp Ser Glu Ala Ile Ala His Asp
325 330 335
Ala Pro Arg Trp Ile Ser Gln Ala Phe Ala Gly Gly Val Lys Cys Ser
340 345 350
Gly Glu Glu Leu Glu Thr Glu Ala Gly Leu His Leu His Leu Asn Tyr
355 360 365
Thr Pro Thr Arg Tyr Asn Gly Glu Asp Val Leu Phe Cys Ala Phe Ser
370 375 380
Glu Ile Ser Ala Arg Lys Arg Met Glu Ala Glu Leu Ala Arg Ala Lys
385 390 395 400
Ser Leu Ala Asp Ala Ala Asn Glu Ala Lys Thr Leu Phe Leu Ala Thr
405 410 415
Met Ser His Glu Ile Arg Thr Pro Leu Tyr Gly Met Leu Gly Thr Leu
420 425 430
Glu Leu Leu Gly Arg Thr Glu Leu Ser Arg Gln Gln Ala Gly Tyr Leu
435 440 445
Lys Ala Ile Gln His Ser Ser Ser Thr Leu Leu Gln Leu Ile Ser Asp
450 455 460
Val Leu Asp Val Ser Lys Ile Glu Ala Gly Gln Leu Asp Leu Glu Cys
465 470 475 480
Val Glu Phe Ser Pro Leu Glu Leu Thr Glu Glu Val Val Gln Ser Phe
485 490 495
Thr Gly Ala Ala Gln Ala Lys Gly Leu Gln Leu Tyr Thr Cys Leu Ser
500 505 510
Ala Glu Leu Pro Leu Arg Met Arg Gly Ala Ala Ala Ser Ile Arg Gln
515 520 525
Ile Leu Asn Asn Leu Leu Ser Asn Ala Val Lys Phe Thr Asp Asn Gly
530 535 540
Tyr Val Asn Val His Leu Lys Ala Ser Val Val Asp Ala Glu Cys Val
545 550 555 560
Met Leu Thr Trp Gln Val Asn Asp Thr Gly Met Gly Ile Asn Val Glu
565 570 575
Asp Gln Pro Arg Leu Phe Glu Pro Phe Tyr Gln Ile Arg Arg Ser Glu
580 585 590
His Pro Val Ala Gly Thr Gly Leu Gly Leu Ser Ile Ser Gln Arg Leu
595 600 605
Ala Gln Leu Met Asn Gly Ser Leu Lys Leu Val Ser Glu Leu Gly Leu
610 615 620
Gly Ser Ser Phe Ser Leu Arg Leu Pro Leu Glu Arg Ile Ala Met Gln
625 630 635 640
Ala Glu Pro Gln Asp Leu Ala Gly Cys Ala Val Gln Val Leu Ala Pro
645 650 655
Val Arg Asp Leu Thr Glu Cys Leu Cys Gly Trp Ile Ser Arg Trp Gly
660 665 670
Gly Arg Ala Met Val Ala Thr Pro Arg Ser Leu Asp Glu Ala Asp Ala
675 680 685
Thr Ser Leu Leu Val Glu Val Leu Leu Leu Glu Gly Ala Pro Met Phe
690 695 700
Glu Ala Trp Pro Gly Cys Arg Val Glu Leu Ser Pro Gln Gly Asp Met
705 710 715 720
Glu Pro Gln Ala Gln Gly Arg Asp Trp Leu Leu Gly Leu Asn Asn Leu
725 730 735
Asp Gly Leu His Arg Ala Leu Gly Leu Ala His Gly Arg Leu Ala Asp
740 745 750
Pro Ser Thr Pro Pro Ile Arg Leu Ala Pro Leu Arg Asn Leu Gly Leu
755 760 765
Arg Val Leu Val Val Glu Asp Asn Ala Ile Asn Gln Leu Ile Leu Arg
770 775 780

```
Asp Gln Met Glu Ala Leu Gly Cys Ser Val Glu Leu Leu Phe Asp Gly
785                 790                 795                 800
Arg Glu Ala Leu Leu His Cys Gln Thr Ala Cys Phe Asp Val Val Leu
                805                 810                 815
Thr Asp Ile Asn Met Pro Asn Met Asn Gly Tyr Glu Leu Thr Ala Glu
            820                 825                 830
Leu Arg Arg Gln Gly Phe Arg Gln Pro Ile Ile Gly Ala Thr Ala Asn
        835                 840                 845
Ala Met Arg Glu Glu Arg Glu Arg Cys Met Ser Ala Gly Met Asn Asp
    850                 855                 860
Cys Leu Val Lys Pro Val Asp Leu Asn Ala Leu Gln Asn Cys Leu Ile
865                 870                 875                 880
Asn Ile Leu Lys Val Asp Arg
                885
```

<210> 23
<211> 874
<212> PRT
<213> Pseudomonas aeruginosa PA14

<400> 23

```
Met Asn Val Ala Met Tyr Glu Ala Gln Leu Tyr Phe Glu Gln Arg Glu
 1               5                  10                  15
Ala Leu Leu Asn His Leu Ser Gly Asn Val Val Pro Leu Ala Ala Gly
            20                  25                  30
Arg Ala Leu Val Asn Glu Ala Pro Asn Asn Val Ser Ile Leu Pro Leu
        35                  40                  45
Ser Asp Gly Gly Arg Gly Leu Leu Leu Thr Ala Arg Thr Leu Gly Asp
    50                  55                  60
Leu Arg Glu Lys Arg Leu Ala Leu Met Tyr Leu Val Asp Thr Asp Lys
65                  70                  75                  80
Gly Pro Leu Val Tyr Arg Leu Thr Ala Asp Gly Arg Pro Ser Ala Ala
                85                  90                  95
Ile Ser Ser Thr Ile Thr Lys Glu Val Tyr Arg Ala Leu Leu Ala Thr
            100                 105                 110
Pro Ser Ala Pro Val His Trp Val Thr Asp Gly Gly Thr Pro Gln Arg
        115                 120                 125
Leu Tyr Leu Phe Glu Ser Leu Gly Asp Glu Pro Gly Glu Gly Trp Leu
    130                 135                 140
Gly Leu Glu Ile Leu Gly Glu Asp Leu Asp Ser Met Leu Arg Arg Asn
145                 150                 155                 160
Asp Ala Gly Asn Tyr Met Leu Leu Asp Gln His Gly Gln Val Val Leu
                165                 170                 175
Ala Thr Asp Ala Glu Ala Leu Gly Ser Gly Ala Ser Arg Thr Leu Leu
            180                 185                 190
Arg Gly Asp Gly Phe Gly Phe Ile Gly Ala Gly Pro Leu Pro Gln His
        195                 200                 205
Met Val Leu Phe Gln His Val Gly Ser Ser Ser Trp Asp Leu Ile Tyr
    210                 215                 220
His Ile Gly Ile Gly Arg Leu Leu Leu Ala Leu Trp Leu Pro Leu Leu
225                 230                 235                 240
Leu Ala Ser Ala Leu Ala Leu Ala Val Gly Ile Leu Leu His Trp Leu
                245                 250                 255
Val Arg Ser Ile Glu Arg Arg Leu Ile Glu Pro Ala Lys Arg Arg Leu
            260                 265                 270
Glu Ala Leu Lys Glu Ser Glu Ala Phe Ser Arg Ala Val Ile Gln Ala
        275                 280                 285
```

```
Ala Pro Val Ala Leu Cys Val Leu Arg Arg Ala Asp Ala Ala Val Val
    290                 295                 300
Leu Glu Asn Pro Gln Ala Arg Gln Trp Leu Gly Asp Ser Glu Ala Ile
305                 310                 315                 320
Ala His Asp Ala Pro Arg Trp Ile Ser Gln Ala Phe Ala Gly Gly Val
                325                 330                 335
Lys Cys Ser Gly Glu Glu Leu Glu Thr Glu Ala Gly Leu His Leu His
            340                 345                 350
Leu Asn Tyr Thr Pro Thr Arg Tyr Asn Gly Glu Asp Val Leu Phe Cys
        355                 360                 365
Ala Phe Ser Glu Ile Ser Ala Arg Lys Arg Met Glu Ala Glu Leu Ala
    370                 375                 380
Arg Ala Lys Ser Leu Ala Asp Ala Ala Asn Glu Ala Lys Thr Leu Phe
385                 390                 395                 400
Leu Ala Thr Met Ser His Glu Ile Arg Thr Pro Leu Tyr Gly Met Leu
                405                 410                 415
Gly Thr Leu Glu Leu Leu Gly Arg Thr Glu Leu Ser Arg Gln Gln Ala
            420                 425                 430
Gly Tyr Leu Lys Ala Ile Gln His Ser Ser Ser Thr Leu Leu Gln Leu
        435                 440                 445
Ile Ser Asp Val Leu Asp Val Ser Lys Ile Glu Ala Gly Gln Leu Asp
    450                 455                 460
Leu Glu Cys Val Glu Phe Ser Pro Leu Glu Leu Thr Glu Glu Val Val
465                 470                 475                 480
Gln Ser Phe Thr Gly Ala Ala Gln Ala Lys Gly Leu Gln Leu Tyr Thr
                485                 490                 495
Cys Leu Ser Ala Glu Leu Pro Leu Arg Met Arg Gly Ala Ala Ala Ser
            500                 505                 510
Ile Arg Gln Ile Leu Asn Asn Leu Leu Ser Asn Ala Val Lys Phe Thr
        515                 520                 525
Asp Asn Gly Tyr Val Asn Val His Leu Lys Ala Ser Val Val Asp Ala
    530                 535                 540
Glu Cys Val Met Leu Thr Trp Gln Val Asn Asp Thr Gly Met Gly Ile
545                 550                 555                 560
Asn Val Glu Asp Gln Pro Arg Leu Phe Glu Pro Phe Tyr Gln Ile Arg
                565                 570                 575
Arg Ser Glu His Pro Val Ala Gly Thr Gly Leu Gly Leu Ser Ile Ser
            580                 585                 590
Gln Arg Leu Ala Gln Leu Met Asn Gly Ser Leu Lys Leu Val Ser Glu
        595                 600                 605
Leu Gly Leu Gly Ser Ser Phe Ser Leu Arg Leu Pro Leu Glu Arg Ile
    610                 615                 620
Ala Met Gln Ala Glu Pro Gln Asp Leu Ala Gly Cys Ala Val Gln Val
625                 630                 635                 640
Leu Ala Pro Val Arg Asp Leu Thr Glu Cys Leu Cys Gly Trp Ile Ser
                645                 650                 655
Arg Trp Gly Gly Arg Ala Met Val Ala Thr Pro Arg Ser Leu Asp Glu
            660                 665                 670
Ala Asp Ala Thr Ser Leu Leu Val Glu Val Leu Leu Leu Glu Gly Ala
        675                 680                 685
Pro Met Phe Glu Ala Trp Pro Gly Cys Arg Val Glu Leu Ser Pro Gln
    690                 695                 700
Gly Asp Met Glu Pro Gln Ala Gln Gly Arg Asp Trp Leu Leu Gly Leu
705                 710                 715                 720
Asn Asn Leu Asp Gly Leu His Arg Ala Leu Gly Leu Ala His Gly Arg
                725                 730                 735
Leu Ala Asp Pro Ser Thr Pro Pro Ile Arg Leu Ala Pro Leu Arg Asn
            740                 745                 750
```

```
Leu Gly Leu Arg Val Leu Val Val Glu Asp Asn Ala Ile Asn Gln Leu
        755                 760                 765
Ile Leu Arg Asp Gln Met Glu Ala Leu Gly Cys Ser Val Glu Leu Leu
    770                 775                 780
Phe Asp Gly Arg Glu Ala Leu Leu His Cys Gln Thr Ala Cys Phe Asp
785                 790                 795                 800
Val Val Leu Thr Asp Ile Asn Met Pro Asn Met Asn Gly Tyr Glu Leu
                805                 810                 815
Thr Ala Glu Leu Arg Arg Gln Gly Phe Arg Gln Pro Ile Ile Gly Ala
            820                 825                 830
Thr Ala Asn Ala Met Arg Glu Glu Arg Glu Arg Cys Met Ser Ala Gly
        835                 840                 845
Met Asn Asp Cys Leu Val Lys Pro Val Asp Leu Asn Ala Leu Gln Asn
    850                 855                 860
Cys Leu Ile Asn Ile Leu Lys Val Asp Arg
865                 870
```

<210> 24
<211> 870
<212> PRT
<213> Pseudomonas aeruginosa PA14

<400> 24

```
Met Tyr Glu Ala Gln Leu Tyr Phe Glu Gln Arg Glu Ala Leu Leu Asn
 1                   5                  10                  15
His Leu Ser Gly Asn Val Val Pro Leu Ala Ala Gly Arg Ala Leu Val
            20                  25                  30
Asn Glu Ala Pro Asn Asn Val Ser Ile Leu Pro Leu Ser Asp Gly Gly
        35                  40                  45
Arg Gly Leu Leu Leu Thr Ala Arg Thr Leu Gly Asp Leu Arg Glu Lys
    50                  55                  60
Arg Leu Ala Leu Met Tyr Leu Val Asp Thr Asp Lys Gly Pro Leu Val
65                  70                  75                  80
Tyr Arg Leu Thr Ala Asp Gly Arg Pro Ser Ala Ala Ile Ser Ser Thr
                85                  90                  95
Ile Thr Lys Glu Val Tyr Arg Ala Leu Leu Ala Thr Pro Ser Ala Pro
            100                 105                 110
Val His Trp Val Thr Asp Gly Gly Thr Pro Gln Arg Leu Tyr Leu Phe
        115                 120                 125
Glu Ser Leu Gly Asp Glu Pro Gly Glu Gly Trp Leu Gly Leu Glu Ile
    130                 135                 140
Leu Gly Glu Asp Leu Asp Ser Met Leu Arg Arg Asn Asp Ala Gly Asn
145                 150                 155                 160
Tyr Met Leu Leu Asp Gln His Gly Gln Val Val Leu Ala Thr Asp Ala
                165                 170                 175
Glu Ala Leu Gly Ser Gly Ala Ser Arg Thr Leu Leu Arg Gly Asp Gly
            180                 185                 190
Phe Gly Phe Ile Gly Ala Gly Pro Leu Pro Gln His Met Val Leu Phe
        195                 200                 205
Gln His Val Gly Ser Ser Ser Trp Asp Leu Ile Tyr His Ile Gly Ile
    210                 215                 220
Gly Arg Leu Leu Leu Ala Leu Trp Leu Pro Leu Leu Leu Ala Ser Ala
225                 230                 235                 240
Leu Ala Leu Ala Val Gly Ile Leu Leu His Trp Leu Val Arg Ser Ile
                245                 250                 255
Glu Arg Arg Leu Ile Glu Pro Ala Lys Arg Arg Leu Glu Ala Leu Lys
            260                 265                 270
```

```
Glu Ser Glu Ala Phe Ser Arg Ala Val Ile Gln Ala Ala Pro Val Ala
        275                 280                 285
Leu Cys Val Leu Arg Arg Ala Asp Ala Ala Val Val Leu Glu Asn Pro
    290                 295                 300
Gln Ala Arg Gln Trp Leu Gly Asp Ser Glu Ala Ile Ala His Asp Ala
305                 310                 315                 320
Pro Arg Trp Ile Ser Gln Ala Phe Ala Gly Gly Val Lys Cys Ser Gly
                325                 330                 335
Glu Glu Leu Glu Thr Glu Ala Gly Leu His Leu His Leu Asn Tyr Thr
            340                 345                 350
Pro Thr Arg Tyr Asn Gly Glu Asp Val Leu Phe Cys Ala Phe Ser Glu
        355                 360                 365
Ile Ser Ala Arg Lys Arg Met Glu Ala Glu Leu Ala Arg Ala Lys Ser
    370                 375                 380
Leu Ala Asp Ala Ala Asn Glu Ala Lys Thr Leu Phe Leu Ala Thr Met
385                 390                 395                 400
Ser His Glu Ile Arg Thr Pro Leu Tyr Gly Met Leu Gly Thr Leu Glu
                405                 410                 415
Leu Leu Gly Arg Thr Glu Leu Ser Arg Gln Gln Ala Gly Tyr Leu Lys
            420                 425                 430
Ala Ile Gln His Ser Ser Ser Thr Leu Leu Gln Leu Ile Ser Asp Val
        435                 440                 445
Leu Asp Val Ser Lys Ile Glu Ala Gly Gln Leu Asp Leu Glu Cys Val
    450                 455                 460
Glu Phe Ser Pro Leu Glu Leu Thr Glu Glu Val Val Gln Ser Phe Thr
465                 470                 475                 480
Gly Ala Ala Gln Ala Lys Gly Leu Gln Leu Tyr Thr Cys Leu Ser Ala
                485                 490                 495
Glu Leu Pro Leu Arg Met Arg Gly Ala Ala Ala Ser Ile Arg Gln Ile
            500                 505                 510
Leu Asn Asn Leu Leu Ser Asn Ala Val Lys Phe Thr Asp Asn Gly Tyr
        515                 520                 525
Val Asn Val His Leu Lys Ala Ser Val Val Asp Ala Glu Cys Val Met
    530                 535                 540
Leu Thr Trp Gln Val Asn Asp Thr Gly Met Gly Ile Asn Val Glu Asp
545                 550                 555                 560
Gln Pro Arg Leu Phe Glu Pro Phe Tyr Gln Ile Arg Arg Ser Glu His
                565                 570                 575
Pro Val Ala Gly Thr Gly Leu Gly Leu Ser Ile Ser Gln Arg Leu Ala
            580                 585                 590
Gln Leu Met Asn Gly Ser Leu Lys Leu Val Ser Glu Leu Gly Leu Gly
        595                 600                 605
Ser Ser Phe Ser Leu Arg Leu Pro Leu Glu Arg Ile Ala Met Gln Ala
    610                 615                 620
Glu Pro Gln Asp Leu Ala Gly Cys Ala Val Gln Val Leu Ala Pro Val
625                 630                 635                 640
Arg Asp Leu Thr Glu Cys Leu Cys Gly Trp Ile Ser Arg Trp Gly Gly
                645                 650                 655
Arg Ala Met Val Ala Thr Pro Arg Ser Leu Asp Glu Ala Asp Ala Thr
            660                 665                 670
Ser Leu Leu Val Glu Val Leu Leu Leu Glu Gly Ala Pro Met Phe Glu
        675                 680                 685
Ala Trp Pro Gly Cys Arg Val Glu Leu Ser Pro Gln Gly Asp Met Glu
    690                 695                 700
Pro Gln Ala Gln Gly Arg Asp Trp Leu Leu Gly Leu Asn Asn Leu Asp
705                 710                 715                 720
Gly Leu His Arg Ala Leu Gly Leu Ala His Gly Arg Leu Ala Asp Pro
                725                 730                 735
```

```
Ser Thr Pro Pro Ile Arg Leu Ala Pro Leu Arg Asn Leu Gly Leu Arg
            740                 745                 750
Val Leu Val Val Glu Asp Asn Ala Ile Asn Gln Leu Ile Leu Arg Asp
        755                 760                 765
Gln Met Glu Ala Leu Gly Cys Ser Val Glu Leu Leu Phe Asp Gly Arg
    770                 775                 780
Glu Ala Leu Leu His Cys Gln Thr Ala Cys Phe Asp Val Val Leu Thr
785                 790                 795                 800
Asp Ile Asn Met Pro Asn Met Asn Gly Tyr Glu Leu Thr Ala Glu Leu
                805                 810                 815
Arg Arg Gln Gly Phe Arg Gln Pro Ile Ile Gly Ala Thr Ala Asn Ala
            820                 825                 830
Met Arg Glu Glu Arg Glu Arg Cys Met Ser Ala Gly Met Asn Asp Cys
        835                 840                 845
Leu Val Lys Pro Val Asp Leu Asn Ala Leu Gln Asn Cys Leu Ile Asn
    850                 855                 860
Ile Leu Lys Val Asp Arg
865                 870
```

<210> 25
<211> 802
<212> PRT
<213> Pseudomonas aeruginosa PA14

<400> 25

```
Met Tyr Leu Val Asp Thr Asp Lys Gly Pro Leu Val Tyr Arg Leu Thr
 1               5                  10                  15
Ala Asp Gly Arg Pro Ser Ala Ala Ile Ser Ser Thr Ile Thr Lys Glu
            20                  25                  30
Val Tyr Arg Ala Leu Leu Ala Thr Pro Ser Ala Pro Val His Trp Val
        35                  40                  45
Thr Asp Gly Gly Thr Pro Gln Arg Leu Tyr Leu Phe Glu Ser Leu Gly
    50                  55                  60
Asp Glu Pro Gly Glu Gly Trp Leu Gly Leu Glu Ile Leu Gly Glu Asp
65                  70                  75                  80
Leu Asp Ser Met Leu Arg Arg Asn Asp Ala Gly Asn Tyr Met Leu Leu
                85                  90                  95
Asp Gln His Gly Gln Val Val Leu Ala Thr Asp Ala Glu Ala Leu Gly
            100                 105                 110
Ser Gly Ala Ser Arg Thr Leu Leu Arg Gly Asp Gly Phe Gly Phe Ile
        115                 120                 125
Gly Ala Gly Pro Leu Pro Gln His Met Val Leu Phe Gln His Val Gly
    130                 135                 140
Ser Ser Ser Trp Asp Leu Ile Tyr His Ile Gly Ile Gly Arg Leu Leu
145                 150                 155                 160
Leu Ala Leu Trp Leu Pro Leu Leu Leu Ala Ser Ala Leu Ala Leu Ala
                165                 170                 175
Val Gly Ile Leu Leu His Trp Leu Val Arg Ser Ile Glu Arg Arg Leu
            180                 185                 190
Ile Glu Pro Ala Lys Arg Arg Leu Glu Ala Leu Lys Glu Ser Glu Ala
        195                 200                 205
Phe Ser Arg Ala Val Ile Gln Ala Ala Pro Val Ala Leu Cys Val Leu
    210                 215                 220
Arg Arg Ala Asp Ala Ala Val Val Leu Glu Asn Pro Gln Ala Arg Gln
225                 230                 235                 240
Trp Leu Gly Asp Ser Glu Ala Ile Ala His Asp Ala Pro Arg Trp Ile
                245                 250                 255
```

```
Ser Gln Ala Phe Ala Gly Gly Val Lys Cys Ser Gly Glu Glu Leu Glu
            260                 265                 270
Thr Glu Ala Gly Leu His Leu His Leu Asn Tyr Thr Pro Thr Arg Tyr
        275                 280                 285
Asn Gly Glu Asp Val Leu Phe Cys Ala Phe Ser Glu Ile Ser Ala Arg
    290                 295                 300
Lys Arg Met Glu Ala Glu Leu Ala Arg Ala Lys Ser Leu Ala Asp Ala
305                 310                 315                 320
Ala Asn Glu Ala Lys Thr Leu Phe Leu Ala Thr Met Ser His Glu Ile
                325                 330                 335
Arg Thr Pro Leu Tyr Gly Met Leu Gly Thr Leu Glu Leu Leu Gly Arg
            340                 345                 350
Thr Glu Leu Ser Arg Gln Gln Ala Gly Tyr Leu Lys Ala Ile Gln His
        355                 360                 365
Ser Ser Ser Thr Leu Leu Gln Leu Ile Ser Asp Val Leu Asp Val Ser
    370                 375                 380
Lys Ile Glu Ala Gly Gln Leu Asp Leu Glu Cys Val Glu Phe Ser Pro
385                 390                 395                 400
Leu Glu Leu Thr Glu Glu Val Val Gln Ser Phe Thr Gly Ala Ala Gln
                405                 410                 415
Ala Lys Gly Leu Gln Leu Tyr Thr Cys Leu Ser Ala Glu Leu Pro Leu
            420                 425                 430
Arg Met Arg Gly Ala Ala Ala Ser Ile Arg Gln Ile Leu Asn Asn Leu
        435                 440                 445
Leu Ser Asn Ala Val Lys Phe Thr Asp Asn Gly Tyr Val Asn Val His
    450                 455                 460
Leu Lys Ala Ser Val Val Asp Ala Glu Cys Val Met Leu Thr Trp Gln
465                 470                 475                 480
Val Asn Asp Thr Gly Met Gly Ile Asn Val Glu Asp Gln Pro Arg Leu
                485                 490                 495
Phe Glu Pro Phe Tyr Gln Ile Arg Arg Ser Glu His Pro Val Ala Gly
            500                 505                 510
Thr Gly Leu Gly Leu Ser Ile Ser Gln Arg Leu Ala Gln Leu Met Asn
        515                 520                 525
Gly Ser Leu Lys Leu Val Ser Glu Leu Gly Leu Gly Ser Ser Phe Ser
    530                 535                 540
Leu Arg Leu Pro Leu Glu Arg Ile Ala Met Gln Ala Glu Pro Gln Asp
545                 550                 555                 560
Leu Ala Gly Cys Ala Val Gln Val Leu Ala Pro Val Arg Asp Leu Thr
                565                 570                 575
Glu Cys Leu Cys Gly Trp Ile Ser Arg Trp Gly Gly Arg Ala Met Val
            580                 585                 590
Ala Thr Pro Arg Ser Leu Asp Glu Ala Asp Ala Thr Ser Leu Leu Val
        595                 600                 605
Glu Val Leu Leu Leu Glu Gly Ala Pro Met Phe Glu Ala Trp Pro Gly
    610                 615                 620
Cys Arg Val Glu Leu Ser Pro Gln Gly Asp Met Glu Pro Gln Ala Gln
625                 630                 635                 640
Gly Arg Asp Trp Leu Leu Gly Leu Asn Asn Leu Asp Gly Leu His Arg
                645                 650                 655
Ala Leu Gly Leu Ala His Gly Arg Leu Ala Asp Pro Ser Thr Pro Pro
            660                 665                 670
Ile Arg Leu Ala Pro Leu Arg Asn Leu Gly Leu Arg Val Leu Val Val
        675                 680                 685
Glu Asp Asn Ala Ile Asn Gln Leu Ile Leu Arg Asp Gln Met Glu Ala
    690                 695                 700
Leu Gly Cys Ser Val Glu Leu Leu Phe Asp Gly Arg Glu Ala Leu Leu
705                 710                 715                 720
```

```
His Cys Gln Thr Ala Cys Phe Asp Val Val Leu Thr Asp Ile Asn Met
                725                 730                 735
Pro Asn Met Asn Gly Tyr Glu Leu Thr Ala Glu Leu Arg Arg Gln Gly
            740                 745                 750
Phe Arg Gln Pro Ile Ile Gly Ala Thr Ala Asn Ala Met Arg Glu Glu
        755                 760                 765
Arg Glu Arg Cys Met Ser Ala Gly Met Asn Asp Cys Leu Val Lys Pro
    770                 775                 780
Val Asp Leu Asn Ala Leu Gln Asn Cys Leu Ile Asn Ile Leu Lys Val
785                 790                 795                 800
Asp Arg
```

<210> 26
<211> 719
<212> PRT
<213> Pseudomonas aeruginosa PA14

<400> 26

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Met Leu Arg Arg Asn Asp Ala Gly Asn Tyr Met Leu Leu Asp Gln His
 1               5                  10                  15
Gly Gln Val Val Leu Ala Thr Asp Ala Glu Ala Leu Gly Ser Gly Ala
            20                  25                  30
Ser Arg Thr Leu Leu Arg Gly Asp Gly Phe Gly Phe Ile Gly Ala Gly
        35                  40                  45
Pro Leu Pro Gln His Met Val Leu Phe Gln His Val Gly Ser Ser Ser
    50                  55                  60
Trp Asp Leu Ile Tyr His Ile Gly Ile Gly Arg Leu Leu Leu Ala Leu
65                  70                  75                  80
Trp Leu Pro Leu Leu Leu Ala Ser Ala Leu Ala Leu Ala Val Gly Ile
                85                  90                  95
Leu Leu His Trp Leu Val Arg Ser Ile Glu Arg Arg Leu Ile Glu Pro
            100                 105                 110
Ala Lys Arg Arg Leu Glu Ala Leu Lys Glu Ser Glu Ala Phe Ser Arg
        115                 120                 125
Ala Val Ile Gln Ala Ala Pro Val Ala Leu Cys Val Leu Arg Arg Ala
    130                 135                 140
Asp Ala Ala Val Val Leu Glu Asn Pro Gln Ala Arg Gln Trp Leu Gly
145                 150                 155                 160
Asp Ser Glu Ala Ile Ala His Asp Ala Pro Arg Trp Ile Ser Gln Ala
                165                 170                 175
Phe Ala Gly Gly Val Lys Cys Ser Gly Glu Glu Leu Glu Thr Glu Ala
            180                 185                 190
Gly Leu His Leu His Leu Asn Tyr Thr Pro Thr Arg Tyr Asn Gly Glu
        195                 200                 205
Asp Val Leu Phe Cys Ala Phe Ser Glu Ile Ser Ala Arg Lys Arg Met
    210                 215                 220
Glu Ala Glu Leu Ala Arg Ala Lys Ser Leu Ala Asp Ala Ala Asn Glu
225                 230                 235                 240
Ala Lys Thr Leu Phe Leu Ala Thr Met Ser His Glu Ile Arg Thr Pro
                245                 250                 255
Leu Tyr Gly Met Leu Gly Thr Leu Glu Leu Leu Gly Arg Thr Glu Leu
            260                 265                 270
Ser Arg Gln Gln Ala Gly Tyr Leu Lys Ala Ile Gln His Ser Ser Ser
        275                 280                 285
Thr Leu Leu Gln Leu Ile Ser Asp Val Leu Asp Val Ser Lys Ile Glu
    290                 295                 300
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Ala Gly Gln Leu Asp Leu Glu Cys Val Glu Phe Ser Pro Leu Glu Leu
305                 310                 315                 320
Thr Glu Glu Val Val Gln Ser Phe Thr Gly Ala Ala Gln Ala Lys Gly
                325                 330                 335
Leu Gln Leu Tyr Thr Cys Leu Ser Ala Glu Leu Pro Leu Arg Met Arg
            340                 345                 350
Gly Ala Ala Ala Ser Ile Arg Gln Ile Leu Asn Asn Leu Leu Ser Asn
        355                 360                 365
Ala Val Lys Phe Thr Asp Asn Gly Tyr Val Asn Val His Leu Lys Ala
    370                 375                 380
Ser Val Val Asp Ala Glu Cys Val Met Leu Thr Trp Gln Val Asn Asp
385                 390                 395                 400
Thr Gly Met Gly Ile Asn Val Glu Asp Gln Pro Arg Leu Phe Glu Pro
                405                 410                 415
Phe Tyr Gln Ile Arg Arg Ser Glu His Pro Val Ala Gly Thr Gly Leu
            420                 425                 430
Gly Leu Ser Ile Ser Gln Arg Leu Ala Gln Leu Met Asn Gly Ser Leu
        435                 440                 445
Lys Leu Val Ser Glu Leu Gly Leu Gly Ser Ser Phe Ser Leu Arg Leu
    450                 455                 460
Pro Leu Glu Arg Ile Ala Met Gln Ala Glu Pro Gln Asp Leu Ala Gly
465                 470                 475                 480
Cys Ala Val Gln Val Leu Ala Pro Val Arg Asp Leu Thr Glu Cys Leu
                485                 490                 495
Cys Gly Trp Ile Ser Arg Trp Gly Gly Arg Ala Met Val Ala Thr Pro
            500                 505                 510
Arg Ser Leu Asp Glu Ala Asp Ala Thr Ser Leu Leu Val Glu Val Leu
        515                 520                 525
Leu Leu Glu Gly Ala Pro Met Phe Glu Ala Trp Pro Gly Cys Arg Val
    530                 535                 540
Glu Leu Ser Pro Gln Gly Asp Met Glu Pro Gln Ala Gln Gly Arg Asp
545                 550                 555                 560
Trp Leu Leu Gly Leu Asn Asn Leu Asp Gly Leu His Arg Ala Leu Gly
                565                 570                 575
Leu Ala His Gly Arg Leu Ala Asp Pro Ser Thr Pro Pro Ile Arg Leu
            580                 585                 590
Ala Pro Leu Arg Asn Leu Gly Leu Arg Val Leu Val Val Glu Asp Asn
        595                 600                 605
Ala Ile Asn Gln Leu Ile Leu Arg Asp Gln Met Glu Ala Leu Gly Cys
    610                 615                 620
Ser Val Glu Leu Leu Phe Asp Gly Arg Glu Ala Leu Leu His Cys Gln
625                 630                 635                 640
Thr Ala Cys Phe Asp Val Val Leu Thr Asp Ile Asn Met Pro Asn Met
                645                 650                 655
Asn Gly Tyr Glu Leu Thr Ala Glu Leu Arg Arg Gln Gly Phe Arg Gln
            660                 665                 670
Pro Ile Ile Gly Ala Thr Ala Asn Ala Met Arg Glu Glu Arg Glu Arg
        675                 680                 685
Cys Met Ser Ala Gly Met Asn Asp Cys Leu Val Lys Pro Val Asp Leu
    690                 695                 700
Asn Ala Leu Gln Asn Cys Leu Ile Asn Ile Leu Lys Val Asp Arg
705                 710                 715
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<210> 27
<211> 709
<212> PRT
<213> Pseudomonas aeruginosa PA14

<400> 27
Met Leu Leu Asp Gln His Gly Gln Val Val Leu Ala Thr Asp Ala Glu
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Ala Leu Gly Ser Gly Ala Ser Arg Thr Leu Leu Arg Gly Asp Gly Phe
20 25 30
Gly Phe Ile Gly Ala Gly Pro Leu Pro Gln His Met Val Leu Phe Gln
35 40 45
His Val Gly Ser Ser Ser Trp Asp Leu Ile Tyr His Ile Gly Ile Gly
50 55 60
Arg Leu Leu Leu Ala Leu Trp Leu Pro Leu Leu Leu Ala Ser Ala Leu
65 70 75 80
Ala Leu Ala Val Gly Ile Leu Leu His Trp Leu Val Arg Ser Ile Glu
85 90 95
Arg Arg Leu Ile Glu Pro Ala Lys Arg Arg Leu Glu Ala Leu Lys Glu
100 105 110
Ser Glu Ala Phe Ser Arg Ala Val Ile Gln Ala Ala Pro Val Ala Leu
115 120 125
Cys Val Leu Arg Arg Ala Asp Ala Ala Val Val Leu Glu Asn Pro Gln
130 135 140
Ala Arg Gln Trp Leu Gly Asp Ser Glu Ala Ile Ala His Asp Ala Pro
145 150 155 160
Arg Trp Ile Ser Gln Ala Phe Ala Gly Gly Val Lys Cys Ser Gly Glu
165 170 175
Glu Leu Glu Thr Glu Ala Gly Leu His Leu His Leu Asn Tyr Thr Pro
180 185 190
Thr Arg Tyr Asn Gly Glu Asp Val Leu Phe Cys Ala Phe Ser Glu Ile
195 200 205
Ser Ala Arg Lys Arg Met Glu Ala Glu Leu Ala Arg Ala Lys Ser Leu
210 215 220
Ala Asp Ala Ala Asn Glu Ala Lys Thr Leu Phe Leu Ala Thr Met Ser
225 230 235 240
His Glu Ile Arg Thr Pro Leu Tyr Gly Met Leu Gly Thr Leu Glu Leu
245 250 255
Leu Gly Arg Thr Glu Leu Ser Arg Gln Gln Ala Gly Tyr Leu Lys Ala
260 265 270
Ile Gln His Ser Ser Ser Thr Leu Leu Gln Leu Ile Ser Asp Val Leu
275 280 285
Asp Val Ser Lys Ile Glu Ala Gly Gln Leu Asp Leu Glu Cys Val Glu
290 295 300
Phe Ser Pro Leu Glu Leu Thr Glu Glu Val Val Gln Ser Phe Thr Gly
305 310 315 320
Ala Ala Gln Ala Lys Gly Leu Gln Leu Tyr Thr Cys Leu Ser Ala Glu
325 330 335
Leu Pro Leu Arg Met Arg Gly Ala Ala Ala Ser Ile Arg Gln Ile Leu
340 345 350
Asn Asn Leu Leu Ser Asn Ala Val Lys Phe Thr Asp Asn Gly Tyr Val
355 360 365
Asn Val His Leu Lys Ala Ser Val Val Asp Ala Glu Cys Val Met Leu
370 375 380
Thr Trp Gln Val Asn Asp Thr Gly Met Gly Ile Asn Val Glu Asp Gln
385 390 395 400
Pro Arg Leu Phe Glu Pro Phe Tyr Gln Ile Arg Arg Ser Glu His Pro
405 410 415
Val Ala Gly Thr Gly Leu Gly Leu Ser Ile Ser Gln Arg Leu Ala Gln
420 425 430
Leu Met Asn Gly Ser Leu Lys Leu Val Ser Glu Leu Gly Leu Gly Ser
435 440 445
Ser Phe Ser Leu Arg Leu Pro Leu Glu Arg Ile Ala Met Gln Ala Glu

```
    450                 455                 460
Pro Gln Asp Leu Ala Gly Cys Ala Val Gln Val Leu Ala Pro Val Arg
465                 470                 475                 480
Asp Leu Thr Glu Cys Leu Cys Gly Trp Ile Ser Arg Trp Gly Gly Arg
                485                 490                 495
Ala Met Val Ala Thr Pro Arg Ser Leu Asp Glu Ala Asp Ala Thr Ser
            500                 505                 510
Leu Leu Val Glu Val Leu Leu Leu Glu Gly Ala Pro Met Phe Glu Ala
        515                 520                 525
Trp Pro Gly Cys Arg Val Glu Leu Ser Pro Gln Gly Asp Met Glu Pro
    530                 535                 540
Gln Ala Gln Gly Arg Asp Trp Leu Leu Gly Leu Asn Asn Leu Asp Gly
545                 550                 555                 560
Leu His Arg Ala Leu Gly Leu Ala His Gly Arg Leu Ala Asp Pro Ser
                565                 570                 575
Thr Pro Pro Ile Arg Leu Ala Pro Leu Arg Asn Leu Gly Leu Arg Val
            580                 585                 590
Leu Val Val Glu Asp Asn Ala Ile Asn Gln Leu Ile Leu Arg Asp Gln
        595                 600                 605
Met Glu Ala Leu Gly Cys Ser Val Glu Leu Leu Phe Asp Gly Arg Glu
    610                 615                 620
Ala Leu Leu His Cys Gln Thr Ala Cys Phe Asp Val Val Leu Thr Asp
625                 630                 635                 640
Ile Asn Met Pro Asn Met Asn Gly Tyr Glu Leu Thr Ala Glu Leu Arg
                645                 650                 655
Arg Gln Gly Phe Arg Gln Pro Ile Ile Gly Ala Thr Ala Asn Ala Met
            660                 665                 670
Arg Glu Glu Arg Glu Arg Cys Met Ser Ala Gly Met Asn Asp Cys Leu
        675                 680                 685
Val Lys Pro Val Asp Leu Asn Ala Leu Gln Asn Cys Leu Ile Asn Ile
    690                 695                 700
Leu Lys Val Asp Arg
705
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<210> 28
<211> 666
<212> PRT
<213> Pseudomonas aeruginosa PA14

<400> 28

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Met Val Leu Phe Gln His Val Gly Ser Ser Ser Trp Asp Leu Ile Tyr
 1               5                  10                  15
His Ile Gly Ile Gly Arg Leu Leu Leu Ala Leu Trp Leu Pro Leu Leu
            20                  25                  30
Leu Ala Ser Ala Leu Ala Leu Ala Val Gly Ile Leu Leu His Trp Leu
        35                  40                  45
Val Arg Ser Ile Glu Arg Arg Leu Ile Glu Pro Ala Lys Arg Arg Leu
    50                  55                  60
Glu Ala Leu Lys Glu Ser Glu Ala Phe Ser Arg Ala Val Ile Gln Ala
65                  70                  75                  80
Ala Pro Val Ala Leu Cys Val Leu Arg Arg Ala Asp Ala Ala Val Val
                85                  90                  95
Leu Glu Asn Pro Gln Ala Arg Gln Trp Leu Gly Asp Ser Glu Ala Ile
            100                 105                 110
Ala His Asp Ala Pro Arg Trp Ile Ser Gln Ala Phe Ala Gly Gly Val
        115                 120                 125
Lys Cys Ser Gly Glu Glu Leu Glu Thr Glu Ala Gly Leu His Leu His
```

```
    130                 135                 140
Leu Asn Tyr Thr Pro Thr Arg Tyr Asn Gly Glu Asp Val Leu Phe Cys
145                 150                 155                 160
Ala Phe Ser Glu Ile Ser Ala Arg Lys Arg Met Glu Ala Glu Leu Ala
                165                 170                 175
Arg Ala Lys Ser Leu Ala Asp Ala Ala Asn Glu Ala Lys Thr Leu Phe
            180                 185                 190
Leu Ala Thr Met Ser His Glu Ile Arg Thr Pro Leu Tyr Gly Met Leu
        195                 200                 205
Gly Thr Leu Glu Leu Leu Gly Arg Thr Glu Leu Ser Arg Gln Gln Ala
    210                 215                 220
Gly Tyr Leu Lys Ala Ile Gln His Ser Ser Ser Thr Leu Leu Gln Leu
225                 230                 235                 240
Ile Ser Asp Val Leu Asp Val Ser Lys Ile Glu Ala Gly Gln Leu Asp
                245                 250                 255
Leu Glu Cys Val Glu Phe Ser Pro Leu Glu Leu Thr Glu Glu Val Val
            260                 265                 270
Gln Ser Phe Thr Gly Ala Ala Gln Ala Lys Gly Leu Gln Leu Tyr Thr
        275                 280                 285
Cys Leu Ser Ala Glu Leu Pro Leu Arg Met Arg Gly Ala Ala Ala Ser
    290                 295                 300
Ile Arg Gln Ile Leu Asn Asn Leu Leu Ser Asn Ala Val Lys Phe Thr
305                 310                 315                 320
Asp Asn Gly Tyr Val Asn Val His Leu Lys Ala Ser Val Val Asp Ala
                325                 330                 335
Glu Cys Val Met Leu Thr Trp Gln Val Asn Asp Thr Gly Met Gly Ile
            340                 345                 350
Asn Val Glu Asp Gln Pro Arg Leu Phe Glu Pro Phe Tyr Gln Ile Arg
        355                 360                 365
Arg Ser Glu His Pro Val Ala Gly Thr Gly Leu Gly Leu Ser Ile Ser
    370                 375                 380
Gln Arg Leu Ala Gln Leu Met Asn Gly Ser Leu Lys Leu Val Ser Glu
385                 390                 395                 400
Leu Gly Leu Gly Ser Ser Phe Ser Leu Arg Leu Pro Leu Glu Arg Ile
                405                 410                 415
Ala Met Gln Ala Glu Pro Gln Asp Leu Ala Gly Cys Ala Val Gln Val
            420                 425                 430
Leu Ala Pro Val Arg Asp Leu Thr Glu Cys Leu Cys Gly Trp Ile Ser
        435                 440                 445
Arg Trp Gly Gly Arg Ala Met Val Ala Thr Pro Arg Ser Leu Asp Glu
    450                 455                 460
Ala Asp Ala Thr Ser Leu Leu Val Glu Val Leu Leu Leu Glu Gly Ala
465                 470                 475                 480
Pro Met Phe Glu Ala Trp Pro Gly Cys Arg Val Glu Leu Ser Pro Gln
                485                 490                 495
Gly Asp Met Glu Pro Gln Ala Gln Gly Arg Asp Trp Leu Leu Gly Leu
            500                 505                 510
Asn Asn Leu Asp Gly Leu His Arg Ala Leu Gly Leu Ala His Gly Arg
        515                 520                 525
Leu Ala Asp Pro Ser Thr Pro Pro Ile Arg Leu Ala Pro Leu Arg Asn
    530                 535                 540
Leu Gly Leu Arg Val Leu Val Val Glu Asp Asn Ala Ile Asn Gln Leu
545                 550                 555                 560
Ile Leu Arg Asp Gln Met Glu Ala Leu Gly Cys Ser Val Glu Leu Leu
                565                 570                 575
Phe Asp Gly Arg Glu Ala Leu Leu His Cys Gln Thr Ala Cys Phe Asp
            580                 585                 590
Val Val Leu Thr Asp Ile Asn Met Pro Asn Met Asn Gly Tyr Glu Leu
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595 600 605
Thr Ala Glu Leu Arg Arg Gln Gly Phe Arg Gln Pro Ile Ile Gly Ala
610 615 620
Thr Ala Asn Ala Met Arg Glu Glu Arg Glu Arg Cys Met Ser Ala Gly
625 630 635 640
Met Asn Asp Cys Leu Val Lys Pro Val Asp Leu Asn Ala Leu Gln Asn
645 650 655
Cys Leu Ile Asn Ile Leu Lys Val Asp Arg
660 665

<210> 29
<211> 496
<212> PRT
<213> Pseudomonas aeruginosa PA14

<400> 29
Met Glu Ala Glu Leu Ala Arg Ala Lys Ser Leu Ala Asp Ala Ala Asn
1 5 10 15
Glu Ala Lys Thr Leu Phe Leu Ala Thr Met Ser His Glu Ile Arg Thr
20 25 30
Pro Leu Tyr Gly Met Leu Gly Thr Leu Glu Leu Leu Gly Arg Thr Glu
35 40 45
Leu Ser Arg Gln Gln Ala Gly Tyr Leu Lys Ala Ile Gln His Ser Ser
50 55 60
Ser Thr Leu Leu Gln Leu Ile Ser Asp Val Leu Asp Val Ser Lys Ile
65 70 75 80
Glu Ala Gly Gln Leu Asp Leu Glu Cys Val Glu Phe Ser Pro Leu Glu
85 90 95
Leu Thr Glu Glu Val Val Gln Ser Phe Thr Gly Ala Ala Gln Ala Lys
100 105 110
Gly Leu Gln Leu Tyr Thr Cys Leu Ser Ala Glu Leu Pro Leu Arg Met
115 120 125
Arg Gly Ala Ala Ala Ser Ile Arg Gln Ile Leu Asn Asn Leu Leu Ser
130 135 140
Asn Ala Val Lys Phe Thr Asp Asn Gly Tyr Val Asn Val His Leu Lys
145 150 155 160
Ala Ser Val Val Asp Ala Glu Cys Val Met Leu Thr Trp Gln Val Asn
165 170 175
Asp Thr Gly Met Gly Ile Asn Val Glu Asp Gln Pro Arg Leu Phe Glu
180 185 190
Pro Phe Tyr Gln Ile Arg Arg Ser Glu His Pro Val Ala Gly Thr Gly
195 200 205
Leu Gly Leu Ser Ile Ser Gln Arg Leu Ala Gln Leu Met Asn Gly Ser
210 215 220
Leu Lys Leu Val Ser Glu Leu Gly Leu Gly Ser Ser Phe Ser Leu Arg
225 230 235 240
Leu Pro Leu Glu Arg Ile Ala Met Gln Ala Glu Pro Gln Asp Leu Ala
245 250 255
Gly Cys Ala Val Gln Val Leu Ala Pro Val Arg Asp Leu Thr Glu Cys
260 265 270
Leu Cys Gly Trp Ile Ser Arg Trp Gly Gly Arg Ala Met Val Ala Thr
275 280 285
Pro Arg Ser Leu Asp Glu Ala Asp Ala Thr Ser Leu Leu Val Glu Val
290 295 300
Leu Leu Leu Glu Gly Ala Pro Met Phe Glu Ala Trp Pro Gly Cys Arg
305 310 315 320
Val Glu Leu Ser Pro Gln Gly Asp Met Glu Pro Gln Ala Gln Gly Arg

```
                325                 330                 335
Asp Trp Leu Leu Gly Leu Asn Asn Leu Asp Gly Leu His Arg Ala Leu
            340                 345                 350
Gly Leu Ala His Gly Arg Leu Ala Asp Pro Ser Thr Pro Pro Ile Arg
        355                 360                 365
Leu Ala Pro Leu Arg Asn Leu Gly Leu Arg Val Leu Val Val Glu Asp
    370                 375                 380
Asn Ala Ile Asn Gln Leu Ile Leu Arg Asp Gln Met Glu Ala Leu Gly
385                 390                 395                 400
Cys Ser Val Glu Leu Leu Phe Asp Gly Arg Glu Ala Leu Leu His Cys
                405                 410                 415
Gln Thr Ala Cys Phe Asp Val Val Leu Thr Asp Ile Asn Met Pro Asn
            420                 425                 430
Met Asn Gly Tyr Glu Leu Thr Ala Glu Leu Arg Arg Gln Gly Phe Arg
        435                 440                 445
Gln Pro Ile Ile Gly Ala Thr Ala Asn Ala Met Arg Glu Glu Arg Glu
    450                 455                 460
Arg Cys Met Ser Ala Gly Met Asn Asp Cys Leu Val Lys Pro Val Asp
465                 470                 475                 480
Leu Asn Ala Leu Gln Asn Cys Leu Ile Asn Ile Leu Lys Val Asp Arg
                485                 490                 495
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<210> 30
<211> 1992
<212> DNA
<213> Pseudomonas aeruginosa PA14

<400> 30

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aacggattag cggtctatga gggacgggag ttttcctttg ctatgccatt tctactggct 180
accaagcacg cgttgagcgc cgattcctcg ggagatccgt tttcgctcgg tgtattgctc 240
gccaatttct acggaagctt ctggagtgtt tccgcctatc ccgcgccaca gttactgatc 300
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tcggcgctgg agatgttggg agtcgcccgg gttgatctgc cggaaacact ctggtggcac 540
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ttcgaacagt tggttgagcg cccggcattc gattcgtaca gcctggtatc gccggatggc 660
gaggtattgc tcggcgcggc ccctgcgacc ggcctgaggg atggcctgaa cctcacccga 720
caggggtcg ccgttcaact gcgcagccag cctgagaacg gctggctcgc ggtctaccga 780
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gtattcaacg acatcacggt ccactgcgag gcggagaccg cgctgtccaa tgcgaagcga 1260
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ggcttcgaag aaagcgttct gttcgaggtt gctggtggct cggtcggcca tttcgaagag 1680
ggtgtcgtcg gcgttgtcga acaacgcctg caacgcctgt ttcagctgca gcgccgcctt 1740
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gtcgcgcacc tgcacgagga tgaccggcag gcgccccgct ccggcgttcg gcgacggctc 1800
ggaagcgacc ctggtcaggt gcaccacatt ggcatcgttc tgcatcggga ctctcctgcc 1860
accctcgcgg ccgcgcatgg aatggcaaaa atcgggcaca gaggatcgat tggcgtcgtc 1920
cgtaacgtca atttccaggc gtcaaaaaca agtatctaca ttcattatag agatactttc 1980
aaatctagat ag 1992

<210> 31
<211> 1830
<212> DNA
<213> Pseudomonas aeruginosa PA14

<400> 31
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gcgccacagt tactgatctt tgatctttcc ggcagcaccc gcctggcagt gccgtcgatt 180
ccctccacag cgcagcgtga caggttgagc ggaagctatc cgatgatagt cgagcgcatt 240
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gctgatcgct atcgcgactc ggcgctggag atgttgggag tcgcccgggt tgatctgccg 360
gaaacactct ggtggcacga cgagccgaac catctgatca tcgctgcgag cctgcttgat 420
ctcaggcgaa tcaatgactt cgaacagttg gttgagcgcc cggcattcga ttcgtacagc 480
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gcaggtctgc tgctgacccc ggcgctgctc ctggccggtt ggctcgggat gcgttggtac 720
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tttgccgcca gcgccatggc caaggacctg caggtagacc cgctcgatac tcttgcgctt 1440
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gtcggccatt tcgaagaggg tgtcgtcggc gttgtcgaac aacgcctgca acgcctgttt 1560
cagctgcagc gccgccttgt cgcgcacctg cacgaggatg accggcaggc gccccgctcc 1620
ggcgttcggc gacggctcgg aagcgaccct ggtcaggtgc accacattgg catcgttctg 1680
catcgggact ctcctgccac cctcgcggcc gcgcatggaa tggcaaaaat cgggcacaga 1740
ggatcgattg gcgtcgtccg taacgtcaat ttccaggcgt caaaaacaag tatctacatt 1800
cattatagag atactttcaa atctagatag 1830

<210> 32
<211> 1608
<212> DNA
<213> Pseudomonas aeruginosa PA14

<400> 32
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cgtgtccatt ggatacgcgc tgatcgctat cgcgactcgg cgctggagat gttgggagtc 120
gcccgggttg atctgccgga aacactctgg tggcacgacg agccgaacca tctgatcatc 180
gctgcgagcc tgcttgatct caggcgaatc aatgacttcg aacagttggt tgagcgcccg 240
gcattcgatt cgtacagcct ggtatcgccg gatggcgagg tattgctcgg cgcggccct 300
gcgaccggcc tgagggatgg cctgaacctc acccgacagg gggtcgccgt tcaactgcgc 360
agccagcctg agaacggctg gctcgcggtc taccgaaccg actacggcaa tttctttcgc 420
cactcccggt ggctggtggc aggtctgctg ctgaccccgg cgctgctcct ggccggttgg 480

ctcgggatgc gttggtacac cagcagcgtc gtcaacccgg tgcatcgggc gcaccggcaa 540
ctggtggaga gcgacacctt cagccggacg ctgatacaga ccgcgccggt ggctctggtg 600
gtgctgaccc aggatgacca gcaactggtg acctgcaacc acttggccgc ccagtggctg 660
ggcgggccca cggagatcct tgggctgact tccaactgga agcttttcga tgcgcgtggg 720
caggtaccag gagacatctg tatccaggtc ggtgggcgct atttgcagac cgccttcgcg 780
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aagaccctgt tcctggcccg catgagccat gaaatccgta ctcccctgta cggtgtcctt 960
ggcaccctgg agttgctcga cctgaccacc ctgaacgagc ggcaacgcgc ctacctacgc 1020
accatccaga gttcgtctgc gacgctcatg caactgatta gcgatgtgct ggatgtctcg 1080
aagatcgaag cggggcagat ggctctgacc ctggccgcct tcaatccgct ggacctagtg 1140
cgggaagtgc ttggcaactt tgccgccagc gccatggcca aggacctgca ggtagacccg 1200
ctcgatactc ttgcgcttga ggcgcaggtc gcgcatggct tcgaagaaag cgttctgttc 1260
gaggttgctg gtggctcggt cggccatttc gaagagggtg tcgtcggcgt tgtcgaacaa 1320
cgcctgcaac gcctgtttca gctgcagcgc cgccttgtcg cgcacctgca cgaggatgac 1380
cggcaggcgc cccgctccgg cgttcggcga cggctcggaa gcgaccctgg tcaggtgcac 1440
cacattggca tcgttctgca tcgggactct cctgccaccc tcgcggccgc gcatggaatg 1500
gcaaaaatcg ggcacagagg atcgattggc gtcgtccgta acgtcaattt ccaggcgtca 1560
aaaacaagta tctacattca ttatagagat actttcaaat ctagatag 1608

<210> 33
<211> 1500
<212> DNA
<213> Pseudomonas aeruginosa PA14

<400> 33
atgttgggag tcgcccgggt tgatctgccg gaaacactct ggtggcacga cgagccgaac 60
catctgatca tcgctgcgag cctgcttgat ctcaggcgaa tcaatgactt cgaacagttg 120
gttgagcgcc cggcattcga ttcgtacagc ctggtatcgc cggatggcga ggtattgctc 180
ggcgcggccc ctgcgaccgg cctgagggat ggcctgaacc tcacccgaca gggggtcgcc 240
gttcaactgc gcagccagcc tgagaacggc tggctcgcgg tctaccgaac cgactacggc 300
aatttctttc gccactcccg gtggctggtg gcaggtctgc tgctgacccc ggcgctgctc 360
ctggccggtt ggctcgggat gcgttggtac accagcagcg tcgtcaaccc ggtgcatcgg 420
gcgcaccggc aactggtgga gagcgacacc ttcagccgga cgctgataca gaccgcgccg 480
gtggctctgg tggtgctgac ccaggatgac cagcaactgg tgacctgcaa ccacttggcc 540
gcccagtggc tgggcgggcc cacggagatc cttgggctga cttccaactg gaagcttttc 600
gatgcgcgtg ggcaggtacc aggagacatc tgtatccagg tcggtgggcg ctatttgcag 660
accgccttcg cggcgacccg ctatgccggc accgaggcgg tactgtgcgt attcaacgac 720
atcacggtcc actgcgaggc ggagaccgcg ctgtccaatg cgaagcgagc agcggatgcc 780
gccagccagg ccaagaccct gttcctggcc cgcatgagcc atgaaatccg tactcccctg 840
tacggtgtcc ttggcaccct ggagttgctc gacctgacca ccctgaacga gcggcaacgc 900
gcctacctac gcaccatcca gagttcgtct gcgacgctca tgcaactgat tagcgatgtg 960
ctggatgtct cgaagatcga agcggggcag atggctctga ccctggccgc cttcaatccg 1020
ctggacctag tgcgggaagt gcttggcaac tttgccgcca gcgccatggc caaggacctg 1080
caggtagacc cgctcgatac tcttgcgctt gaggcgcagg tcgcgcatgg cttcgaagaa 1140
agcgttctgt tcgaggttgc tggtggctcg gtcggccatt tcgaagaggg tgtcgtcggc 1200
gttgtcgaac aacgcctgca acgcctgttt cagctgcagc gccgccttgt cgcgcacctg 1260
cacgaggatg accggcaggc gccccgctcc ggcgttcggc gacggctcgg aagcgaccct 1320
ggtcaggtgc accacattgg catcgttctg catcgggact ctcctgccac cctcgcggcc 1380
gcgcatggaa tggcaaaaat cgggcacaga ggatcgattg gcgtcgtccg taacgtcaat 1440
ttccaggcgt caaaaacaag tatctacatt cattatagag atactttcaa atctagatag 1500

<210> 34
<211> 1122
<212> DNA
<213> Pseudomonas aeruginosa PA14

<400> 34
atgcgttggt acaccagcag cgtcgtcaac ccggtgcatc gggcgcaccg gcaactggtg 60
gagagcgaca ccttcagccg gacgctgata cagaccgcgc cggtggctct ggtggtgctg 120
acccaggatg accagcaact ggtgacctgc aaccacttgg ccgcccagtg gctgggcggg 180
cccacggaga tccttgggct gacttccaac tggaagcttt tcgatgcgcg tgggcaggta 240
ccaggagaca tctgtatcca ggtcggtggg cgctatttgc agaccgcctt cgcggcgacc 300
cgctatgccg gcaccgaggc ggtactgtgc gtattcaacg acatcacggt ccactgcgag 360
gcggagaccg cgctgtccaa tgcgaagcga gcagcggatg ccgccagcca ggccaagacc 420
ctgttcctgg cccgcatgag ccatgaaatc cgtactcccc tgtacggtgt ccttggcacc 480
ctggagttgc tcgacctgac caccctgaac gagcggcaac gcgcctacct acgcaccatc 540
cagagttcgt ctgcgacgct catgcaactg attagcgatg tgctggatgt ctcgaagatc 600
gaagcggggc agatggctct gaccctggcc gccttcaatc cgctggacct agtgcgggaa 660
gtgcttggca actttgccgc cagcgccatg gccaaggacc tgcaggtaga cccgctcgat 720
actcttgcgc ttgaggcgca ggtcgcgcat ggcttcgaag aaagcgttct gttcgaggtt 780
gctggtggct cggtcggcca tttcgaagag ggtgtcgtcg gcgttgtcga acaacgcctg 840
caacgcctgt ttcagctgca gcgccgcctt gtcgcgcacc tgcacgagga tgaccggcag 900
gcgccccgct ccggcgttcg gcgacggctc ggaagcgacc ctggtcaggt gcaccacatt 960
ggcatcgttc tgcatcggga ctctcctgcc accctcgcgg ccgcgcatgg aatggcaaaa 1020
atcgggcaca gaggatcgat tggcgtcgtc cgtaacgtca atttccaggc gtcaaaaaca 1080
agtatctaca ttcattatag agatactttc aaatctagat ag 1122

<210> 35
<211> 663
<212> PRT
<213> Pseudomonas aeruginosa PA14

<400> 35
Met Asp Val Ile Arg Glu His Glu Val Phe Leu Gly Arg Ile Ala Arg
1 5 10 15
Lys Ser Asp Lys Thr Thr Gln Lys Tyr Asp Tyr Asp Val Val Pro Leu
20 25 30
Gln Arg His Leu Leu Ala Lys Glu Asn Gly Leu Ala Val Tyr Glu Gly
35 40 45
Arg Glu Phe Ser Phe Ala Met Pro Phe Leu Leu Ala Thr Lys His Ala
50 55 60
Leu Ser Ala Asp Ser Ser Gly Asp Pro Phe Ser Leu Gly Val Leu Leu
65 70 75 80
Ala Asn Phe Tyr Gly Ser Phe Trp Ser Val Ser Ala Tyr Pro Ala Pro
85 90 95
Gln Leu Leu Ile Phe Asp Leu Ser Gly Ser Thr Arg Leu Ala Val Pro
100 105 110
Ser Ile Pro Ser Thr Ala Gln Arg Asp Arg Leu Ser Gly Ser Tyr Pro
115 120 125
Met Ile Val Glu Arg Ile Leu Ala Arg Leu Arg Thr Arg Pro Val Gly
130 135 140
Glu Asp Ala Gln Arg Val His Trp Ile Arg Ala Asp Arg Tyr Arg Asp
145 150 155 160
Ser Ala Leu Glu Met Leu Gly Val Ala Arg Val Asp Leu Pro Glu Thr
165 170 175
Leu Trp Trp His Asp Glu Pro Asn His Leu Ile Ile Ala Ala Ser Leu
180 185 190
Leu Asp Leu Arg Arg Ile Asn Asp Phe Glu Gln Leu Val Glu Arg Pro
195 200 205
Ala Phe Asp Ser Tyr Ser Leu Val Ser Pro Asp Gly Glu Val Leu Leu
210 215 220
Gly Ala Ala Pro Ala Thr Gly Leu Arg Asp Gly Leu Asn Leu Thr Arg
225 230 235 240
Gln Gly Val Ala Val Gln Leu Arg Ser Gln Pro Glu Asn Gly Trp Leu

```
                245                 250                 255
Ala Val Tyr Arg Thr Asp Tyr Gly Asn Phe Phe Arg His Ser Arg Trp
            260                 265                 270
Leu Val Ala Gly Leu Leu Leu Thr Pro Ala Leu Leu Leu Ala Gly Trp
        275                 280                 285
Leu Gly Met Arg Trp Tyr Thr Ser Ser Val Val Asn Pro Val His Arg
    290                 295                 300
Ala His Arg Gln Leu Val Glu Ser Asp Thr Phe Ser Arg Thr Leu Ile
305                 310                 315                 320
Gln Thr Ala Pro Val Ala Leu Val Val Leu Thr Gln Asp Asp Gln Gln
                325                 330                 335
Leu Val Thr Cys Asn His Leu Ala Ala Gln Trp Leu Gly Gly Pro Thr
            340                 345                 350
Glu Ile Leu Gly Leu Thr Ser Asn Trp Lys Leu Phe Asp Ala Arg Gly
        355                 360                 365
Gln Val Pro Gly Asp Ile Cys Ile Gln Val Gly Gly Arg Tyr Leu Gln
    370                 375                 380
Thr Ala Phe Ala Ala Thr Arg Tyr Ala Gly Thr Glu Ala Val Leu Cys
385                 390                 395                 400
Val Phe Asn Asp Ile Thr Val His Cys Glu Ala Glu Thr Ala Leu Ser
                405                 410                 415
Asn Ala Lys Arg Ala Ala Asp Ala Ala Ser Gln Ala Lys Thr Leu Phe
            420                 425                 430
Leu Ala Arg Met Ser His Glu Ile Arg Thr Pro Leu Tyr Gly Val Leu
        435                 440                 445
Gly Thr Leu Glu Leu Leu Asp Leu Thr Thr Leu Asn Glu Arg Gln Arg
    450                 455                 460
Ala Tyr Leu Arg Thr Ile Gln Ser Ser Ser Ala Thr Leu Met Gln Leu
465                 470                 475                 480
Ile Ser Asp Val Leu Asp Val Ser Lys Ile Glu Ala Gly Gln Met Ala
                485                 490                 495
Leu Thr Leu Ala Ala Phe Asn Pro Leu Asp Leu Val Arg Glu Val Leu
            500                 505                 510
Gly Asn Phe Ala Ala Ser Ala Met Ala Lys Asp Leu Gln Val Asp Pro
        515                 520                 525
Leu Asp Thr Leu Ala Leu Glu Ala Gln Val Ala His Gly Phe Glu Glu
    530                 535                 540
Ser Val Leu Phe Glu Val Ala Gly Gly Ser Val Gly His Phe Glu Glu
545                 550                 555                 560
Gly Val Val Gly Val Val Glu Gln Arg Leu Gln Arg Leu Phe Gln Leu
                565                 570                 575
Gln Arg Arg Leu Val Ala His Leu His Glu Asp Asp Arg Gln Ala Pro
            580                 585                 590
Arg Ser Gly Val Arg Arg Arg Leu Gly Ser Asp Pro Gly Gln Val His
        595                 600                 605
His Ile Gly Ile Val Leu His Arg Asp Ser Pro Ala Thr Leu Ala Ala
    610                 615                 620
Ala His Gly Met Ala Lys Ile Gly His Arg Gly Ser Ile Gly Val Val
625                 630                 635                 640
Arg Asn Val Asn Phe Gln Ala Ser Lys Thr Ser Ile Tyr Ile His Tyr
                645                 650                 655
Arg Asp Thr Phe Lys Ser Arg
            660
```

<210> 36
<211> 609
<212> PRT

<213> Pseudomonas aeruginosa PA14

<400> 36

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Met Pro Phe Leu Leu Ala Thr Lys His Ala Leu Ser Ala Asp Ser Ser
 1               5                  10                  15
Gly Asp Pro Phe Ser Leu Gly Val Leu Leu Ala Asn Phe Tyr Gly Ser
            20                  25                  30
Phe Trp Ser Val Ser Ala Tyr Pro Ala Pro Gln Leu Leu Ile Phe Asp
        35                  40                  45
Leu Ser Gly Ser Thr Arg Leu Ala Val Pro Ser Ile Pro Ser Thr Ala
    50                  55                  60
Gln Arg Asp Arg Leu Ser Gly Ser Tyr Pro Met Ile Val Glu Arg Ile
65                  70                  75                  80
Leu Ala Arg Leu Arg Thr Arg Pro Val Gly Glu Asp Ala Gln Arg Val
                85                  90                  95
His Trp Ile Arg Ala Asp Arg Tyr Arg Asp Ser Ala Leu Glu Met Leu
            100                 105                 110
Gly Val Ala Arg Val Asp Leu Pro Glu Thr Leu Trp Trp His Asp Glu
        115                 120                 125
Pro Asn His Leu Ile Ile Ala Ala Ser Leu Leu Asp Leu Arg Arg Ile
    130                 135                 140
Asn Asp Phe Glu Gln Leu Val Glu Arg Pro Ala Phe Asp Ser Tyr Ser
145                 150                 155                 160
Leu Val Ser Pro Asp Gly Glu Val Leu Leu Gly Ala Ala Pro Ala Thr
                165                 170                 175
Gly Leu Arg Asp Gly Leu Asn Leu Thr Arg Gln Gly Val Ala Val Gln
            180                 185                 190
Leu Arg Ser Gln Pro Glu Asn Gly Trp Leu Ala Val Tyr Arg Thr Asp
        195                 200                 205
Tyr Gly Asn Phe Phe Arg His Ser Arg Trp Leu Val Ala Gly Leu Leu
    210                 215                 220
Leu Thr Pro Ala Leu Leu Leu Ala Gly Trp Leu Gly Met Arg Trp Tyr
225                 230                 235                 240
Thr Ser Ser Val Val Asn Pro Val His Arg Ala His Arg Gln Leu Val
                245                 250                 255
Glu Ser Asp Thr Phe Ser Arg Thr Leu Ile Gln Thr Ala Pro Val Ala
            260                 265                 270
Leu Val Val Leu Thr Gln Asp Asp Gln Gln Leu Val Thr Cys Asn His
        275                 280                 285
Leu Ala Ala Gln Trp Leu Gly Gly Pro Thr Glu Ile Leu Gly Leu Thr
    290                 295                 300
Ser Asn Trp Lys Leu Phe Asp Ala Arg Gly Gln Val Pro Gly Asp Ile
305                 310                 315                 320
Cys Ile Gln Val Gly Gly Arg Tyr Leu Gln Thr Ala Phe Ala Ala Thr
                325                 330                 335
Arg Tyr Ala Gly Thr Glu Ala Val Leu Cys Val Phe Asn Asp Ile Thr
            340                 345                 350
Val His Cys Glu Ala Glu Thr Ala Leu Ser Asn Ala Lys Arg Ala Ala
        355                 360                 365
Asp Ala Ala Ser Gln Ala Lys Thr Leu Phe Leu Ala Arg Met Ser His
    370                 375                 380
Glu Ile Arg Thr Pro Leu Tyr Gly Val Leu Gly Thr Leu Glu Leu Leu
385                 390                 395                 400
Asp Leu Thr Thr Leu Asn Glu Arg Gln Arg Ala Tyr Leu Arg Thr Ile
                405                 410                 415
Gln Ser Ser Ser Ala Thr Leu Met Gln Leu Ile Ser Asp Val Leu Asp
            420                 425                 430
Val Ser Lys Ile Glu Ala Gly Gln Met Ala Leu Thr Leu Ala Ala Phe
```

```
        435                 440                 445
Asn Pro Leu Asp Leu Val Arg Glu Val Leu Gly Asn Phe Ala Ala Ser
    450                 455                 460
Ala Met Ala Lys Asp Leu Gln Val Asp Pro Leu Asp Thr Leu Ala Leu
465                 470                 475                 480
Glu Ala Gln Val Ala His Gly Phe Glu Glu Ser Val Leu Phe Glu Val
                485                 490                 495
Ala Gly Gly Ser Val Gly His Phe Glu Glu Gly Val Val Gly Val Val
            500                 505                 510
Glu Gln Arg Leu Gln Arg Leu Phe Gln Leu Gln Arg Arg Leu Val Ala
        515                 520                 525
His Leu His Glu Asp Asp Arg Gln Ala Pro Arg Ser Gly Val Arg Arg
    530                 535                 540
Arg Leu Gly Ser Asp Pro Gly Gln Val His His Ile Gly Ile Val Leu
545                 550                 555                 560
His Arg Asp Ser Pro Ala Thr Leu Ala Ala Ala His Gly Met Ala Lys
                565                 570                 575
Ile Gly His Arg Gly Ser Ile Gly Val Val Arg Asn Val Asn Phe Gln
            580                 585                 590
Ala Ser Lys Thr Ser Ile Tyr Ile His Tyr Arg Asp Thr Phe Lys Ser
        595                 600                 605
Arg
```

<210> 37
<211> 535
<212> PRT
<213> Pseudomonas aeruginosa PA14

```
<400> 37
Met Ile Val Glu Arg Ile Leu Ala Arg Leu Arg Thr Arg Pro Val Gly
 1               5                  10                  15
Glu Asp Ala Gln Arg Val His Trp Ile Arg Ala Asp Arg Tyr Arg Asp
            20                  25                  30
Ser Ala Leu Glu Met Leu Gly Val Ala Arg Val Asp Leu Pro Glu Thr
        35                  40                  45
Leu Trp Trp His Asp Glu Pro Asn His Leu Ile Ile Ala Ala Ser Leu
    50                  55                  60
Leu Asp Leu Arg Arg Ile Asn Asp Phe Glu Gln Leu Val Glu Arg Pro
65                  70                  75                  80
Ala Phe Asp Ser Tyr Ser Leu Val Ser Pro Asp Gly Glu Val Leu Leu
                85                  90                  95
Gly Ala Ala Pro Ala Thr Gly Leu Arg Asp Gly Leu Asn Leu Thr Arg
            100                 105                 110
Gln Gly Val Ala Val Gln Leu Arg Ser Gln Pro Glu Asn Gly Trp Leu
        115                 120                 125
Ala Val Tyr Arg Thr Asp Tyr Gly Asn Phe Phe Arg His Ser Arg Trp
    130                 135                 140
Leu Val Ala Gly Leu Leu Leu Thr Pro Ala Leu Leu Leu Ala Gly Trp
145                 150                 155                 160
Leu Gly Met Arg Trp Tyr Thr Ser Ser Val Val Asn Pro Val His Arg
                165                 170                 175
Ala His Arg Gln Leu Val Glu Ser Asp Thr Phe Ser Arg Thr Leu Ile
            180                 185                 190
Gln Thr Ala Pro Val Ala Leu Val Val Leu Thr Gln Asp Asp Gln Gln
        195                 200                 205
Leu Val Thr Cys Asn His Leu Ala Ala Gln Trp Leu Gly Gly Pro Thr
```

```
    210                 215                 220
Glu Ile Leu Gly Leu Thr Ser Asn Trp Lys Leu Phe Asp Ala Arg Gly
225                 230                 235                 240
Gln Val Pro Gly Asp Ile Cys Ile Gln Val Gly Gly Arg Tyr Leu Gln
                245                 250                 255
Thr Ala Phe Ala Ala Thr Arg Tyr Ala Gly Thr Glu Ala Val Leu Cys
            260                 265                 270
Val Phe Asn Asp Ile Thr Val His Cys Glu Ala Glu Thr Ala Leu Ser
        275                 280                 285
Asn Ala Lys Arg Ala Ala Asp Ala Ala Ser Gln Ala Lys Thr Leu Phe
    290                 295                 300
Leu Ala Arg Met Ser His Glu Ile Arg Thr Pro Leu Tyr Gly Val Leu
305                 310                 315                 320
Gly Thr Leu Glu Leu Leu Asp Leu Thr Thr Leu Asn Glu Arg Gln Arg
                325                 330                 335
Ala Tyr Leu Arg Thr Ile Gln Ser Ser Ser Ala Thr Leu Met Gln Leu
            340                 345                 350
Ile Ser Asp Val Leu Asp Val Ser Lys Ile Glu Ala Gly Gln Met Ala
        355                 360                 365
Leu Thr Leu Ala Ala Phe Asn Pro Leu Asp Leu Val Arg Glu Val Leu
    370                 375                 380
Gly Asn Phe Ala Ala Ser Ala Met Ala Lys Asp Leu Gln Val Asp Pro
385                 390                 395                 400
Leu Asp Thr Leu Ala Leu Glu Ala Gln Val Ala His Gly Phe Glu Glu
                405                 410                 415
Ser Val Leu Phe Glu Val Ala Gly Gly Ser Val Gly His Phe Glu Glu
            420                 425                 430
Gly Val Val Gly Val Val Glu Gln Arg Leu Gln Arg Leu Phe Gln Leu
        435                 440                 445
Gln Arg Arg Leu Val Ala His Leu His Glu Asp Asp Arg Gln Ala Pro
    450                 455                 460
Arg Ser Gly Val Arg Arg Arg Leu Gly Ser Asp Pro Gly Gln Val His
465                 470                 475                 480
His Ile Gly Ile Val Leu His Arg Asp Ser Pro Ala Thr Leu Ala Ala
                485                 490                 495
Ala His Gly Met Ala Lys Ile Gly His Arg Gly Ser Ile Gly Val Val
            500                 505                 510
Arg Asn Val Asn Phe Gln Ala Ser Lys Thr Ser Ile Tyr Ile His Tyr
        515                 520                 525
Arg Asp Thr Phe Lys Ser Arg
    530                 535
```

<210> 38
<211> 499
<212> PRT
<213> Pseudomonas aeruginosa PA14

<400> 38

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Met Leu Gly Val Ala Arg Val Asp Leu Pro Glu Thr Leu Trp Trp His
 1               5                  10                  15
Asp Glu Pro Asn His Leu Ile Ile Ala Ala Ser Leu Leu Asp Leu Arg
            20                  25                  30
Arg Ile Asn Asp Phe Glu Gln Leu Val Glu Arg Pro Ala Phe Asp Ser
        35                  40                  45
Tyr Ser Leu Val Ser Pro Asp Gly Glu Val Leu Leu Gly Ala Ala Pro
    50                  55                  60
Ala Thr Gly Leu Arg Asp Gly Leu Asn Leu Thr Arg Gln Gly Val Ala
```

```
65                  70                  75                  80
Val Gln Leu Arg Ser Gln Pro Glu Asn Gly Trp Leu Ala Val Tyr Arg
                85                  90                  95
Thr Asp Tyr Gly Asn Phe Phe Arg His Ser Arg Trp Leu Val Ala Gly
            100                 105                 110
Leu Leu Leu Thr Pro Ala Leu Leu Leu Ala Gly Trp Leu Gly Met Arg
        115                 120                 125
Trp Tyr Thr Ser Ser Val Val Asn Pro Val His Arg Ala His Arg Gln
    130                 135                 140
Leu Val Glu Ser Asp Thr Phe Ser Arg Thr Leu Ile Gln Thr Ala Pro
145                 150                 155                 160
Val Ala Leu Val Val Leu Thr Gln Asp Asp Gln Gln Leu Val Thr Cys
                165                 170                 175
Asn His Leu Ala Ala Gln Trp Leu Gly Gly Pro Thr Glu Ile Leu Gly
            180                 185                 190
Leu Thr Ser Asn Trp Lys Leu Phe Asp Ala Arg Gly Gln Val Pro Gly
        195                 200                 205
Asp Ile Cys Ile Gln Val Gly Gly Arg Tyr Leu Gln Thr Ala Phe Ala
    210                 215                 220
Ala Thr Arg Tyr Ala Gly Thr Glu Ala Val Leu Cys Val Phe Asn Asp
225                 230                 235                 240
Ile Thr Val His Cys Glu Ala Glu Thr Ala Leu Ser Asn Ala Lys Arg
                245                 250                 255
Ala Ala Asp Ala Ala Ser Gln Ala Lys Thr Leu Phe Leu Ala Arg Met
            260                 265                 270
Ser His Glu Ile Arg Thr Pro Leu Tyr Gly Val Leu Gly Thr Leu Glu
        275                 280                 285
Leu Leu Asp Leu Thr Thr Leu Asn Glu Arg Gln Arg Ala Tyr Leu Arg
    290                 295                 300
Thr Ile Gln Ser Ser Ser Ala Thr Leu Met Gln Leu Ile Ser Asp Val
305                 310                 315                 320
Leu Asp Val Ser Lys Ile Glu Ala Gly Gln Met Ala Leu Thr Leu Ala
                325                 330                 335
Ala Phe Asn Pro Leu Asp Leu Val Arg Glu Val Leu Gly Asn Phe Ala
            340                 345                 350
Ala Ser Ala Met Ala Lys Asp Leu Gln Val Asp Pro Leu Asp Thr Leu
        355                 360                 365
Ala Leu Glu Ala Gln Val Ala His Gly Phe Glu Glu Ser Val Leu Phe
    370                 375                 380
Glu Val Ala Gly Gly Ser Val Gly His Phe Glu Glu Gly Val Val Gly
385                 390                 395                 400
Val Val Glu Gln Arg Leu Gln Arg Leu Phe Gln Leu Gln Arg Arg Leu
                405                 410                 415
Val Ala His Leu His Glu Asp Asp Arg Gln Ala Pro Arg Ser Gly Val
            420                 425                 430
Arg Arg Arg Leu Gly Ser Asp Pro Gly Gln Val His His Ile Gly Ile
        435                 440                 445
Val Leu His Arg Asp Ser Pro Ala Thr Leu Ala Ala Ala His Gly Met
    450                 455                 460
Ala Lys Ile Gly His Arg Gly Ser Ile Gly Val Val Arg Asn Val Asn
465                 470                 475                 480
Phe Gln Ala Ser Lys Thr Ser Ile Tyr Ile His Tyr Arg Asp Thr Phe
                485                 490                 495
Lys Ser Arg
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<210> 39

<211> 373
<212> PRT
<213> Pseudomonas aeruginosa PA14

<400> 39
Met Arg Trp Tyr Thr Ser Ser Val Val Asn Pro Val His Arg Ala His
1 5 10 15
Arg Gln Leu Val Glu Ser Asp Thr Phe Ser Arg Thr Leu Ile Gln Thr
20 25 30
Ala Pro Val Ala Leu Val Val Leu Thr Gln Asp Asp Gln Gln Leu Val
35 40 45
Thr Cys Asn His Leu Ala Ala Gln Trp Leu Gly Gly Pro Thr Glu Ile
50 55 60
Leu Gly Leu Thr Ser Asn Trp Lys Leu Phe Asp Ala Arg Gly Gln Val
65 70 75 80
Pro Gly Asp Ile Cys Ile Gln Val Gly Gly Arg Tyr Leu Gln Thr Ala
85 90 95
Phe Ala Ala Thr Arg Tyr Ala Gly Thr Glu Ala Val Leu Cys Val Phe
100 105 110
Asn Asp Ile Thr Val His Cys Glu Ala Glu Thr Ala Leu Ser Asn Ala
115 120 125
Lys Arg Ala Ala Asp Ala Ala Ser Gln Ala Lys Thr Leu Phe Leu Ala
130 135 140
Arg Met Ser His Glu Ile Arg Thr Pro Leu Tyr Gly Val Leu Gly Thr
145 150 155 160
Leu Glu Leu Leu Asp Leu Thr Thr Leu Asn Glu Arg Gln Arg Ala Tyr
165 170 175
Leu Arg Thr Ile Gln Ser Ser Ser Ala Thr Leu Met Gln Leu Ile Ser
180 185 190
Asp Val Leu Asp Val Ser Lys Ile Glu Ala Gly Gln Met Ala Leu Thr
195 200 205
Leu Ala Ala Phe Asn Pro Leu Asp Leu Val Arg Glu Val Leu Gly Asn
210 215 220
Phe Ala Ala Ser Ala Met Ala Lys Asp Leu Gln Val Asp Pro Leu Asp
225 230 235 240
Thr Leu Ala Leu Glu Ala Gln Val Ala His Gly Phe Glu Glu Ser Val
245 250 255
Leu Phe Glu Val Ala Gly Gly Ser Val Gly His Phe Glu Glu Gly Val
260 265 270
Val Gly Val Val Glu Gln Arg Leu Gln Arg Leu Phe Gln Leu Gln Arg
275 280 285
Arg Leu Val Ala His Leu His Glu Asp Asp Arg Gln Ala Pro Arg Ser
290 295 300
Gly Val Arg Arg Arg Leu Gly Ser Asp Pro Gly Gln Val His His Ile
305 310 315 320
Gly Ile Val Leu His Arg Asp Ser Pro Ala Thr Leu Ala Ala Ala His
325 330 335
Gly Met Ala Lys Ile Gly His Arg Gly Ser Ile Gly Val Val Arg Asn
340 345 350
Val Asn Phe Gln Ala Ser Lys Thr Ser Ile Tyr Ile His Tyr Arg Asp
355 360 365
Thr Phe Lys Ser Arg
370